*The Banting Memorial Lecture 1959**

The Adrenal and Diabetes

Some Interactions and Interrelations

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Boston

INTRODUCTION

FIG. 1. Sir Frederick G. Banting.

I appreciate, deeply, the honor which has been given to me in being chosen to present this—the Ninth Annual Banting Memorial Lecture of the American Diabetes Association. The list of distinguished investigators which precedes me is evidence of the esteem and admiration in which Banting is held. For the younger members of the Association, who perhaps never knew Sir Frederick Banting, I have reproduced a photograph (figure 1), and a short biographical sketch. It should be appreciated that this young man's career was interrupted by military service (a frequent experience nowadays); nevertheless, he ultimately returned to the laboratory in a department of physiology to pursue an idea—this after completing his clinical training and engaging temporarily in private practice (figure 2).

FREDERICK G. BANTING

1891	Born in Alliston, Ontario, Canada.
1916	M.D. from University of Toronto.
1916-17	Served in France, World War I.
1919	Resident Surgeon in Toronto.
1920	Practice in Medicine in London, Ontario. Assistant in Physiology, Western University.
1921	University of Toronto, Department of Physiology. Research on the secretion of the pancreas.
1923	Nobel Laureate in Medicine.
1930	The Banting Institute of Medical Research.
1934	Knight Commander of the British Empire.
1941	Feb. 21, killed in plane crash in Newfoundland.

FIGURE 2

Dr. Elliott P. Joslin has been kind enough to allow me to reproduce here a page from Banting and Best's laboratory notebook dated Aug. 7, 1921 (figure 3). This is, I believe, the only page of Banting and Best's notes presently preserved outside of Toronto, and it seems fitting that it should be framed on the wall of Dr. Joslin's study.

* **Presented at the Nineteenth Annual Meeting of the American Diabetes Association in Atlantic City on June 6, 1959,** by Dr. George W. Thorn, Hersey Professor of the Theory and Practice of Physic, Harvard Medical School, and Physician in Chief at the Peter Bent Brigham Hospital, Boston, Massachusetts, who was awarded the Banting Medal for 1959.

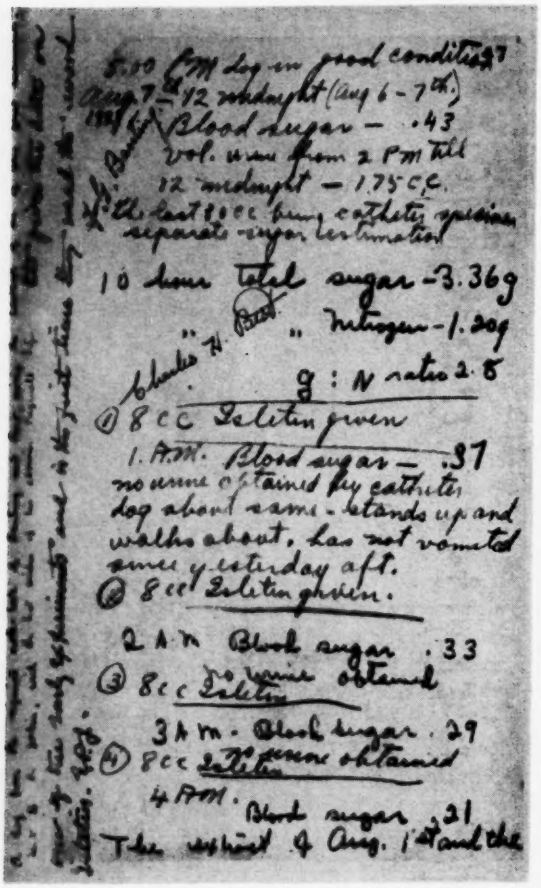
5.00 PM dog in good condition
Aug 7 – 12 midnight (Aug 6 – 7th.)
Blood sugar – .43
Vol. urine from 2 PM till
12 midnight – 1.75 c.c.
10 hour total sugar – 3.36g
" Nitrogen – 1.20g
g : N ratio 2.8
① 8 cc Isletin given
1. A.M. Blood sugar – .37
no urine obtained by catheter
dog about same – stands up and
walks about. Has not vomited
since yesterday aft.
② 8 cc Isletin given.
2 A.M. Blood sugar .33
③ 8 cc Isletin
3 A.M. Blood sugar .29
④ 8 cc Isletin
4 A.M. Blood sugar .21

FIG. 3. Notes on injection of "Isletin" made by Banting and Best, Aug. 7, 1921. Courtesy of Dr. Elliott P. Joslin.

Although I have always maintained a keen interest in diabetes mellitus and the study of intermediary carbohydrate metabolism, I do not wish to conceal the fact that my approach to this field has been over the "steroid" bridge! Historically, the close temporal and geographical relationship which existed between the discovery of insulin and cortin may not be familiar to all of you. Dr. Frank Hartman (figure 4), upon completing his training in 1915 with Professor Walter Cannon at Harvard Medical School, accepted a position as Lecturer and later Assistant Professor in the Department of Physiology at Toronto. In 1919, he was appointed Professor of Physiology at the University of Buffalo Medical School. Two years later (1921) in the Department of Physiology at the University of Toronto, Banting and Best prepared an extract of the pancreas with hypoglycemic activity. Hartman[1] and his co-workers in the Department of Physiology at the University of Buffalo a few years later (1927), reported on an extract of the adrenal cortex which prolonged the life of adrenalectomized cats. It is of further interest, in view of this morning's discussion, to note that in the meantime Dr. Carl Cori had joined Dr. Hartman's Department of Physiology at Buffalo.

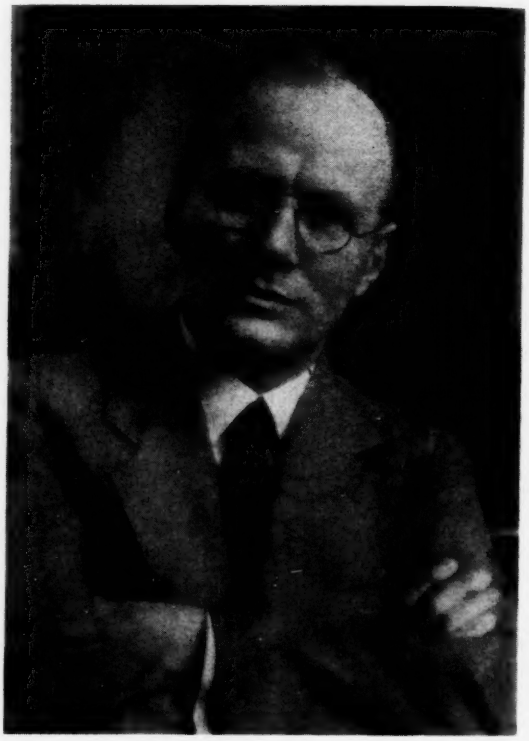

FIG. 4. Frank A. Hartman, Ph.D.

My own introduction to the adrenal and its hypoglycemic symptomatology took place as a medical student in the Department of Physiology at this time, where I enjoyed an association with both Dr. Hartman and Dr. Cori. The warm relationship which existed between the departments of physiology in Toronto and Buffalo in their epoch-making contributions in the 1920's is well epitomized by the Peace Bridge which connects the two Niagara frontiers. Today, the traveling distance between the two departments is less than twenty minutes! Can it be that more than chance conspired in the close geographical and temporal discovery of these two hormones which in the organism provide such a nicely

balanced system in regulating intermediary metabolism? It is also of interest to note that each of these particular hormones has a satellite—hydrocortisone has epinephrine, and insulin has glucagon!

In recent years, a major activity of our Endocrine-Metabolic Unit has been concerned with a study of insulin, the adrenal steroids and their effect on intermediary carbohydrate and fat metabolism. A comparison of the structure and molar concentrations in plasma of the principal hormones of the adrenal and the pancreas (as related to carbohydrate metabolism) is presented in figure 5. The widely differing chemical structure and size of these biologically highly active substances suggest diverse sites and modes of action. The discussion today will be concerned with the effects of epinephrine, ACTH and hydrocortisone on intermediary metabolism. The relation of the action of these hormones to the effects of insulin will also be pointed out, as well as certain clinical implications regarding the role of the adrenal in diabetes mellitus.

EPINEPHRINE AND CARBOHYDRATE METABOLISM

In early studies the injection of whole adrenal extract was characterized by tachycardia and a rise in blood pressure.[2] It was not until the active principle of the adrenal medulla had been isolated (Abel and Crawford),[3] and crystallized (Takamine,[4] Aldrich[5]), that Blum[6] in 1901 reported the occurrence of glycosuria following the subcutaneous injection of adrenal extracts, and termed this condition "adrenalin diabetes." In 1902 and 1903, Metzger,[7] as well as Herter,[8,9] demonstrated that the glycosuria resulted from hyperglycemia. Although an epinephrine effect upon glycogen in liver and muscle was described early, the fact that, depending upon the time interval and the dosage selected, it either decreased or increased hepatic glycogen caused much confusion. Between 1928 and 1930, Cori and Cori[10-12] clearly established the glycogenolytic effect of epinephrine in liver and muscle, with formation of glucose from liver and lactic acid from muscle. They also resolved the previous conflict by demonstrating that the

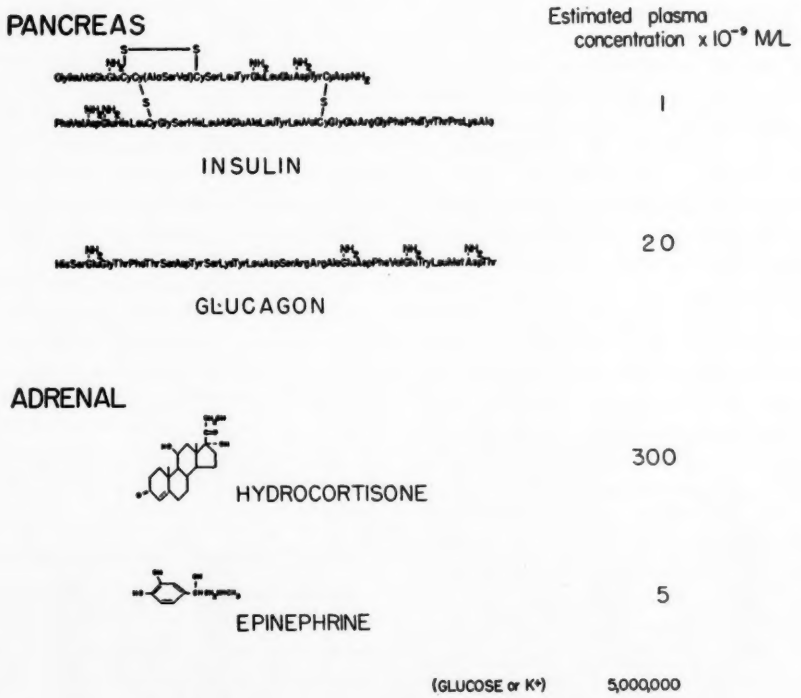

FIG. 5. Chemical formulae and estimated relative plasma concentrations of pancreatic and adrenal hormones. The relative concentration of plasma glucose or potassium on the same scale is 5,000,000 times that of insulin.

late hepatic glycogen accumulation which follows the administration of relatively large doses of epinephrine to fasting animals is the result of reaccumulation of glycogen from lactate liberated by muscle. Finally, Cori and Cori[13] also established that epinephrine decreased glucose utilization by muscle. This fact was later corroborated by the in vitro studies of Walaas and Walaas.[14]

Effects on muscle and liver: In 1937, Cori[15] and his co-workers demonstrated that glucose-1-phosphate (Cori ester) is both the precursor of glycogen synthesis and the product of glycogenolysis (figure 6), the interconversion being catalyzed by the enzyme phosphorylase. The studies of Sutherland[16,17] and others in liver and muscle preparations indicated that the presence of epinephrine resulted in increased phosphorylase activity. Since enzyme activity facilitates the attainment of a given equilibrium, the observation that epinephrine induced glycogenolysis even in metabolic states favoring glycogen synthesis presented a paradox and suggested that phosphorylase primarily catalyzes glycogen breakdown. In 1957, Leloir and Cardini[18] demonstrated that glycogen synthesis may indeed occur by another pathway, not involving phosphorylase. This pathway requires the presence of uridine-di-phosphoglucose (figure 6). Thus, there may well be two pathways for glycogen synthesis, and it is possible—indeed likely—that they independently effect primarily glycogen synthesis (UDPG pathway) and glycogen breakdown (phosphorylase).

Further clarification of the activation of phosphorylase resulted from the extensive studies of Sutherland[17] who in 1951 demonstrated that epinephrine favors conversion of inactive phosphorylase into the active form. He and his collaborators[19] also demonstrated that this activation of phosphorylase, both in liver and in muscle, involves the synthesis of a cyclic adenine nucleotide also shown in figure 6. It would seem, therefore, that the sequence of events in this reaction is as follows: *Epinephrine reacts with tissue components to accelerate the formation of cyclic adenine nucleotide, which in turn accelerates the formation of active phosphorylase and this in turn alters the steady state of the uridine-di-phosphoglucose and phosphorylase systems in favor of glycogenolysis.* It is of some interest to note that glucagon effects the same sequence of reactions, although only in liver.

The epinephrine-induced glycogenolysis in muscle is illustrated in figure 7. Increased glycogen breakdown in this tissue results in the accumulation of phosphorylated intermediates, among which is glucose-6-phosphate. Since glucose-6-phosphate inhibits glucose phosphorylation by hexokinase,[20] decreased "free" glucose utilization results. Glycolysis through the Embden-Meyerhof pathway, however, is greatly accelerated, with the resultant production of large quantities of lactate. In the liver (figure 7), in contrast, accelerated glycogen breakdown results primarily in an increased net outflow of glucose for three reasons: (1) Liver, in contrast to muscle, possesses the enzyme glucose-6-phosphatase which converts glucose-6-phosphate into free glucose. (2) The increased intracellular glucose-6-phosphate concentration in liver, as in muscle, inhibits "free" glucose phosphorylation, thereby favoring net glucose production by the liver. (3) Because of low hepatic phosphofructokinase[21] activity, and high fructose-1,6-diphosphatase activity, liver rarely achieves net glycolysis to lactate, since a relative block thus exists between fructose-6-phosphate and fructose-1,6-diphosphate.

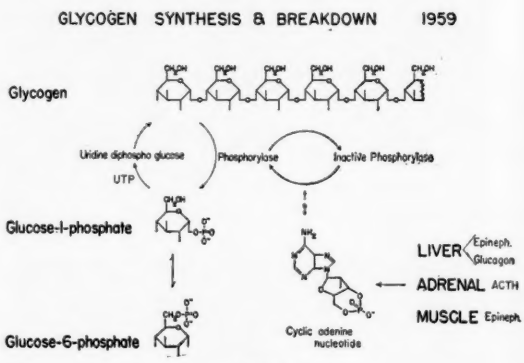

FIGURE 6

In summary, epinephrine action results in enhanced phosphorylase activity and therefore an increased rate of glycogenolysis. Secondarily, the accumulation of phosphorylated intermediates, specifically glucose-6-phosphate, inhibits the conversion of glucose to glucose-6-phosphate. This latter change, in addition to increased hepatic glycogenolysis and glucose output, provides an explanation for the diabetes-like state induced acutely by the hormone.

EPINEPHRINE AND ADIPOSE TISSUE METABOLISM

During the last three years much work in our laboratory has been directed to a study of the effects of hormones upon adipose tissue. In this tissue insulin has been shown to enhance primarily glucose utilization with resultant increased lipid synthesis,[22,23] an energy store analogous to that of glycogen in liver and muscle. As shown in figure 8, this effect of insulin in accelerating

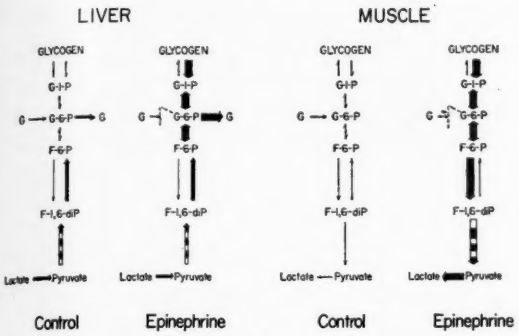

FIG. 7. Effect of epinephrine on liver and muscle glycolysis. G = glucose; G-1-P = glucose-1-phosphate; G-6-P = glucose-6-phosphate; F-6-P = fructose-6-phosphate; F-1,6-di P = fructose-1,6-diphosphate.

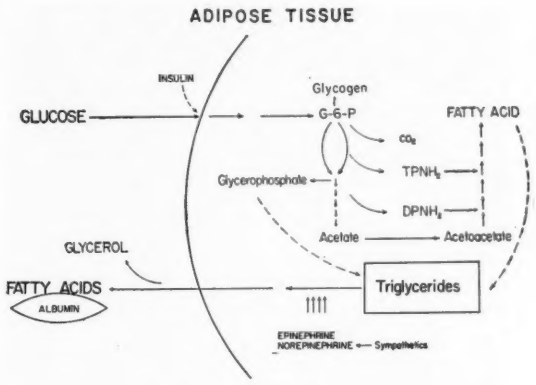

FIGURE 9

the rate of fatty acid synthesis can be readily demonstrated both in vivo and in vitro, and since fatty acid synthesis is associated with an obligatory loss of CO_2 in the conversion of pyruvate to acetate, insulin results in a marked stimulation of CO_2 production. Figure 9 schematically summarizes some of the pathways of fatty acid synthesis in adipose tissue and emphasizes that this synthesis involves the breakdown of glucose-6-phosphate to 2-carbon fragments from which long-chain fatty acids are synthesized. Furthermore, since the formation of fatty acids from acetate is a reductive synthesis, it involves the transfer of hydrogen in the form of both reduced TPN and DPN. The major source of the reduced TPN results from the reactions leading to the direct oxidation of glucose-6-phosphate and the oxidative decarboxylation of 6-phosphogluconate, the so-called "shunt." The schema also illustrates the need for glycerol, derived primarily from glucose in this tissue for the ultimate storage of fatty acids as tri-esters of glycerol.

In contrast to insulin, which primarily leads to increased lipid synthesis, epinephrine facilitates lipid breakdown and release of fatty acids and glycerol into the circulation,[24,25] as shown in figure 10. This effect of epinephrine upon the release of fatty acids from adipose tissue is quite analogous to its glycogenolytic effect in muscle and liver in mobilizing stored metabolic fuels.

From the clinical point of view, it is of interest that loss of body fat is seen in patients with pheochromocytoma when the syndrome is associated with an increased basal metabolic rate and elevated body temperature. Through the courtesy of Dr. Meyer M. Melicow of New York City, who first described this phenomenon, a possible local effect of epinephrine on periadrenal adipose tissue in man is illustrated in figure 11. Dr. Melicow[26] observed in sixteen out of eighteen pheochromocytomas that the adipose tissue surrounding the tumor histologically resembled "brown" adipose tissue, a tissue quite depleted of fat. Adipose tissue surrounding adrenal cortical adenomata or carcinomata, on the

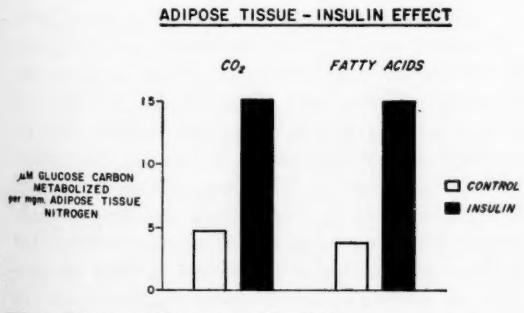

FIG. 8. Data from Winegrad and Renold.[22]

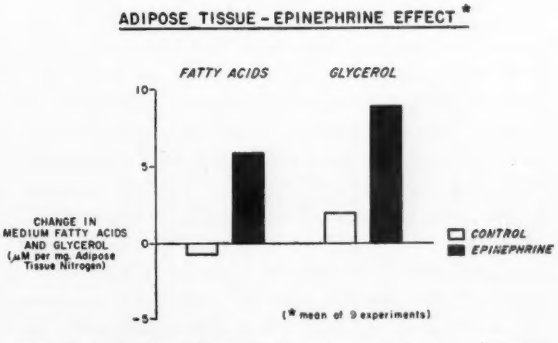

FIG. 10. Data from Cahill et al.[25] and unpublished experiments.

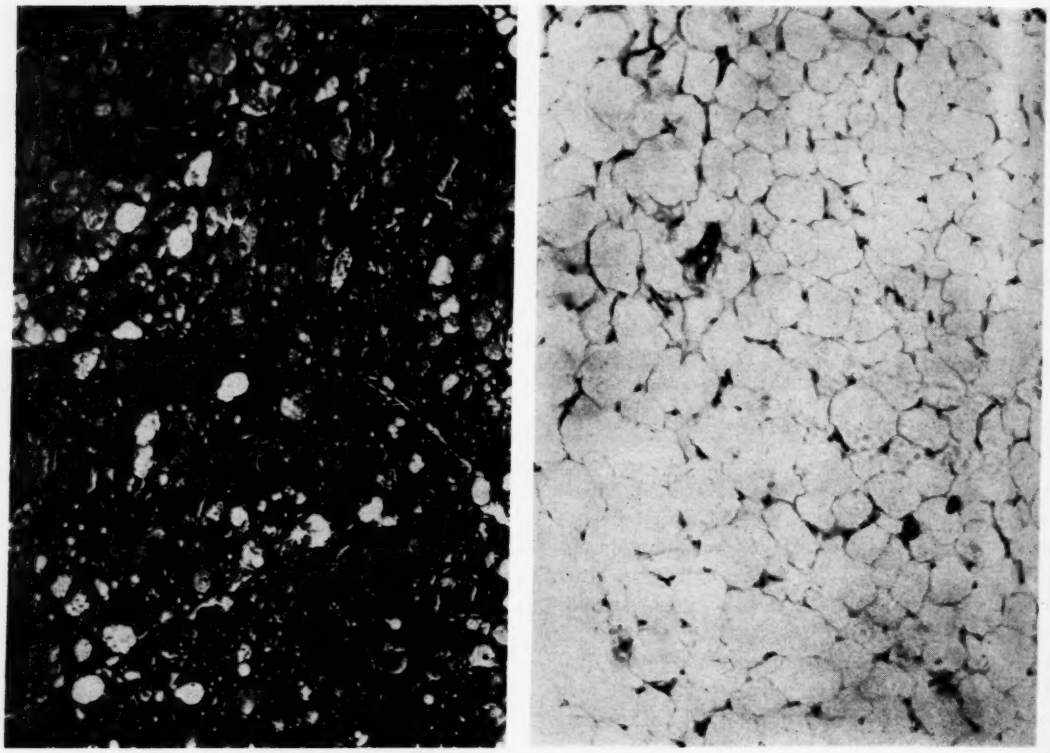

FIG. 11. Comparison of periadrenal fat (left) and fat obtained elsewhere (right) from a patient with a pheochromocytoma. Courtesy of Dr. M. M. Melicow.[26]

other hand, did not show this anomaly nor did other lipid storage sites in patients with pheochromocytoma. It is at least conceivable that this represents a direct effect of epinephrine upon the surrounding adipose tissue, resulting perhaps in persistent fatty acid mobilization and thereby lipid depletion.

As might be expected, the incidence of glucosuria and hyperglycemia in patients with pheochromocytoma varies widely, presumably depending on the relative excess of epinephrine secretion. Hyperglycemia and glucosuria are therefore more likely to be observed in patients who exhibit sweating, tachycardia and an elevated basal metabolic rate, signs of increased epinephrine secretion. However, depletion of adipose reserves in all patients might be anticipated since both epinephrine and norepinephrine are "lipolytic." A study of blood ketone bodies or unesterified fatty acids, under standard conditions, might prove to be helpful in suspecting an associated pheochromocytoma in patients with hypertension. Furthermore, it might be anticipated that obesity in conjunction with hypertension would make the diagnosis of pheochromocytoma unlikely.

ADRENAL CORTEX AND INTERMEDIARY METABOLISM

The probable existence of a direct adrenal cortical influence on carbohydrate metabolism was first suggested in 1908 by Bierry and Malloizel's observation[27] of hypoglycemia in adrenalectomized dogs and Porges'[28] independent description in 1909 of fasting hypoglycemia in patients with Addison's disease. Following the discovery of insulin, Maranon[29] reported in 1925 that patients with adrenal insufficiency exhibited marked sensitivity to insulin and, shortly thereafter, the existence of diminished hepatic glycogen reserves in fasted adrenalectomized animals was conclusively established by Cori.[30] The striking amelioration of the diabetic state following adrenalectomy suggested by Hartman[31] in 1934 was established by Long and Lukens[32] in 1935 and 1936. The then prevailing knowledge was analyzed with particular clarity by Britton and Silvette,[33,34] and in a classic report by Long, Katzin and Fry, in 1940.[35] To the latter investigators it appeared established (a) that *fasted,* adrenalectomized animals showed decreased levels of blood glucose, as well as decreased liver and muscle glycogen, whereas *fed* adrenalectomized animals

maintained on saline did not; (b) that the administration of adrenal cortical extract resulted in increased levels of blood glucose and liver glycogen and increased nitrogen excretion; (c) that these observations could best be interpreted as indicating that adrenalectomized animals were unable to synthesize glucose from endogenous protein sources at a rate sufficient to prevent liver glycogen depletion and hypoglycemia under fasting conditions. As will be seen, this summary still encompasses a large part of what is securely established today! First, however, one should mention a very recent development in adrenal cortical physiology, which concerns the mode of ACTH action upon this tissue.

Carbohydrate metabolism within the adrenal cortex: Haynes[36] has recently shown that ACTH exerts an effect on *adrenal* glycogen similar to that which occurs with epinephrine in liver and muscle and with glucagon in liver. Furthermore, the glycogenolytic activity of ACTH in the adrenal appears to be mediated by the same series of reactions previously shown and illustrated in figure 6. It has been suggested that accelerated glycogen breakdown in adrenal cortical tissue, resulting in accelerated metabolism of glucose-6-phosphate primarily by the phosphogluconate-oxidative pathway, exerts an effect upon steroid synthesis similar to the effect of insulin upon fatty acid synthesis in adipose tissue. In particular, accelerated metabolism of glucose-6-phosphate by way of the phosphogluconate-oxidative pathway would result in increased availability of reduced TPN, a required cofactor both for the synthesis of the carbon skeleton of steroids and for the subsequent hydroxylations necessary to form active hormone. On the other hand, Eickorn, Halkerston, Feinstein, and Hechter just reported an insulin-like effect of ACTH upon the entrance of sugars into adrenal cortical cells.[37]

Glucocorticoid effect of hepatic gluconeogenesis: Although the adrenal cortex secretes several biologically active steroids, the following discussion will be restricted primarily to that of hydrocortisone (Cortisol). Experimental evidence is lacking regarding the effect of adrenal androgens on carbohydrate metabolism, and the effects of corticosterone and aldosterone on intermediary metabolism appear to be qualitatively similar to that of hydrocortisone.

Most of the enzymatic reactions of glycolysis in hepatic tissue are freely reversible. There are, however, three notable exceptions (figure 12): (1) Glucose phosphorylation is catalyzed by hexokinase, while its dephosphorylation is catalyzed by glucose-6-phosphatase. (2) Fructose-6-phosphate is further phosphorylated to fructose-1,6-diphosphate in the presence of phosphofructokinase while the reverse reaction is catalyzed by the enzyme fructose-1,6-diphosphatase. (3) Although phosphoenolpyruvate is freely metabolized to pyruvate, pyruvate encounters energetic difficulties in being reconverted to phosphoenolpyruvate directly, and does so almost exclusively by way of malate (with incorporation of CO_2), oxaloacetate, and subsequent decarboxylation to phosphoenolpyruvate. As particularly emphasized recently by Krebs,[38] these three steps, providing separate reactions upward and downward, would a priori seem to be particularly suitable sites for the exertion of a *directional* control of metabolic flow, since they provide *directional* flow valves. It is therefore of considerable interest to find selectively increased glucose-6-phosphatase activity,[39] increased fructose diphosphatase activity,[40] and increased incorporation of CO_2 into hepatic glycogen and glucose[41] resulting from Cortisol overdosage in experimental animals. These relationships are schematically summarized for the hypoadrenal and the hyperadrenal state in figure 12.

It is of interest that early studies[42] shown in figure 13, had already indicated the effectiveness of adrenal cortical extract in increasing the total synthesis of carbohydrate from pyruvate in liver slices. Very recent experiments (figure 14) carried out by Ashmore, Landau, and Mahler[41] and using either pyruvate-2-C^{14} or

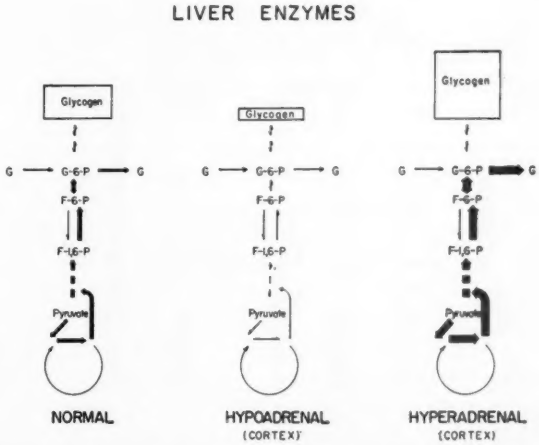

FIG. 12. The "controlling" steps which accelerate the flow of substrate to glucose and glycogen in the hyperadrenal animal and which are depressed in the hypoadrenal animal are respectively the "dicarboxylic acid shuttle" involved in the initial utilization of pyruvate, fructose-1,6-diphosphatase catalyzing the conversion of fructose-1,6-diphosphate (F-1,6-P) to fructose-6-phosphate (F-6-P) and glucose-6-phosphatase, catalyzing the formation of free glucose (G) from glucose-6-phosphate (G-6-P).

$C^{14}O_2$ are particularly impressive and indicated that, in the intact rat treated with large doses of cortisone, the rate of incorporation of these precursors into either blood glucose or liver glycogen increased between ten and a hundredfold.

In summary then, it would seem that an effect of glucocorticoids upon hepatic glucose production from three-carbon precursors represents one of the most firmly established metabolic effects of these hormones. Although established early[42] *it is of considerable interest that with elucidation of the pathways and enzymes involved, it has become possible to document the postulated overall metabolic effect at each of the individual steps which are able to direct the metabolic flow in a specific direction.*

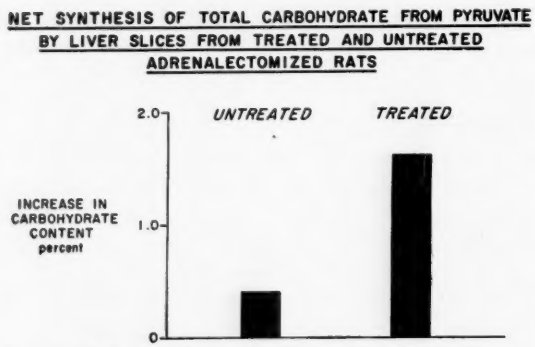

FIG. 13. Data from Koepf, Horn, Gemmill, and Thorn.[42]

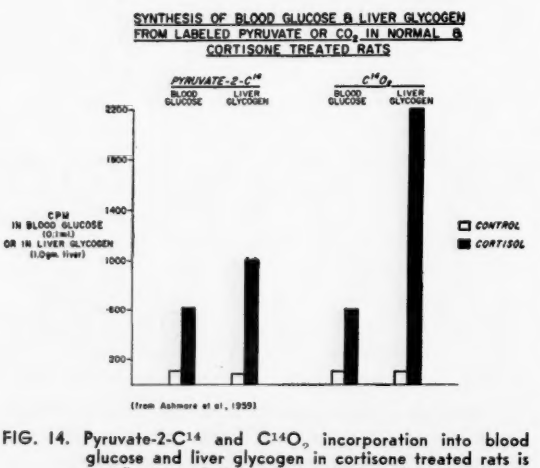

FIG. 14. Pyruvate-2-C^{14} and $C^{14}O_2$ incorporation into blood glucose and liver glycogen in cortisone treated rats is a reflection of the activity of the "dicarboxylic-acid shuttle" since this pathway involves the reductive condensation of CO_2 with pyruvate to form malate. This in turn equilibrates with fumarate and succinate, randomizing the $C^{14}O_2$ label to either end of the molecule. Thus, after the subsequent decarboxylation of oxalacetate, labeled carbon is incorporated into phosphoenolpyruvate which, by the reversal of the glycolytic pathway in liver, is converted into glucose or glycogen.[41]

Observations in man: With regard to glucocorticoid effects on glucose balance, information available in man, although more indirect in nature, agrees remarkably well with the information available in intact animals and their isolated tissues. Patients with Addison's disease exhibit fasting hypoglycemia and subnormal urinary nitrogen excretion, while glucocorticoid administration increases fasting levels of blood glucose as well as the urinary excretion of nitrogen. Furthermore, more definitive evidence for the gluconeogenetic effects of glucocorticoids in the intact organism has been obtained from observations in two fasting subjects with renal glucosuria, observations illustrated in figure 15. In both instances, Cortisol was administered intravenously over eight hours, the subjects having been previously fasted for sixteen hours and continuing to fast throughout the experimental period. In both instances, urinary glucose excretion increased within two hours of the beginning of Cortisol administration and reached maximal rates three and eight times greater than the initial one. Despite this considerably increased urinary glucose loss during fasting, blood glucose levels significantly increased in both subjects. Since it may be safely assumed that in fasting individuals given Cortisol, liver glycogen is increasing and not decreasing, and since in man glucose utilization by tissues such as muscle is known to decrease with fasting, it is reasonable to conclude that increased hepatic gluconeogenesis of the order of magnitude of several grams per hour had resulted in these studies during Cortisol administration.

Recent observations on blood pyruvate, lactate and alpha-ketoglutarate levels in normal subjects, in patients with Cushing's syndrome, and in patients undergoing high-dosage glucocorticoid therapy, have established the interesting fact that elevated values for blood lactate and pyruvate are a characteristic feature of spontaneous or induced hyperadrenocorticism.[43–45] In addition, these observations have been interpreted as indicative of a decreased ability to metabolize pyruvate and it has been suggested that glucocorticoids exert a direct inhibitory effect upon the oxidative decarboxylation of pyruvate in tissues other than the liver, an interpretation which must for the present be considered speculative.

Glucocorticoid effects on protein metabolism: Following Evans'[46] demonstration of increased nitrogen excretion as a result of the administration of adrenal cortical

THE EFFECT OF HYDROCORTISONE ON BLOOD GLUCOSE AND RENAL GLUCOSE CLEARANCE IN TWO FASTED PATIENTS WITH RENAL GLUCOSURIA

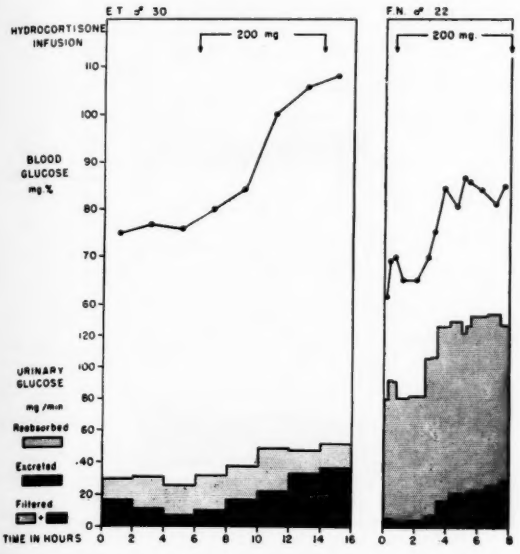

FIG. 15. Data from Froesch, Winegrad, Renold, and Thorn.[64]

extracts, and following the evidence summarized by Britton and Silvette[33,34] in 1932, and Long, Katzin, and Fry[35] in 1940, it has become generally accepted that glucocorticoids increase protein catabolism and/or decrease protein anabolism. Specific evidence more recently accumulated includes (1) a demonstration by Ingle[47] and Bondy[48] that glucocorticoid administration results in increased amino acid release by extrahepatic tissue in hepatectomized animals, (2) the suggestion by Noall, Riggs, Walker, and Christensen[49] that increased catabolism of amino acids might be primarily mediated by enhanced trapping of amino acids by liver and (3) the clear-cut demonstration by Rosen, Roberts, Budnick and Nichol[50] of an increased rate of transamination and increased activity of transaminases in hepatic tissue. All three observations are compatible with the concept of increased mobilization of protein by way of amino acids to the liver, with subsequent transamination and, presumably, conversion to glucose.

From the clinical standpoint it has been early recognized that several important features of hyperadrenalcorticism, as found in Cushing's syndrome, directly suggest the primary importance of an effect of the adrenal cortex upon protein catabolism and/or anabolism. Thus, Cushing's syndrome is associated with marked and widespread protein depletion in muscle and supporting structures (skin, blood vessels and bone) as shown in figure 16. It is of particular interest that such evidence of profound derangement in protein metabolism may be present in these patients before the occurrence of grossly deranged carbohydrate metabolism. In contrast, evidence of specific protein depletion such as osteoporosis is rarely, if ever, found in patients with uncomplicated diabetes mellitus, even if severe in character and of relatively long duration.

Despite the excellence of the evidence accumulated both for increased gluconeogenesis and for protein catabolism as a result of glucocorticoid action, it was early apparent that in patients or animals with glucosuria, the increased glucosuria produced by the administration of adrenal extracts or hydrocortisone could not be accounted for entirely by increased protein catabolism —as reflected by urinary excretion of nitrogen (figure 17). Since it was, and is, generally accepted that significant conversion of fat to glucose does not occur, the assumption was made that glucocorticoid action led to decreased glucose utilization, as well as to increased glucose production.

In reviewing this concept today, it should be pointed out that direct interference with glucose utilization is not the only possible explanation for the discrepancy which exists between glucose and nitrogen excretion. Thus, even in the fasting state, if it is assumed that glycogen stores are almost totally depleted, an increased G/N ratio could result if the protein used for conversion to glucose were a protein with a high polysaccharide content, e.g., protein components of ground substance. The occurrence of temporary nitrogen storage in the form of diamino acids also is conceivable. In the nonfasted state, a decreased *net* glucose utilization by tissues could result from the glucose-sparing action of increased lipid oxidation and from accelerated resynthesis of glucose from three-carbon fragments originally derived from ingested glucose. Finally in the mobilization of fatty acids, glycerol is also made available to the body as a limited source of carbohydrate. Any or all of these mechanisms would favor an increased glucose to nitrogen ratio similar to that which would result from direct interference with glucose utilization. Furthermore, evidence for direct interference with glucose utilization has been difficult to obtain.[51]

Glucocorticoid effects on lipid metabolism: There is no doubt that glucocorticoids exert an important effect on over-all lipid metabolism. Patients with Cushing's syndrome exhibit a striking loss of peripheral adipose tissue with an increase in centrally located fat, particu-

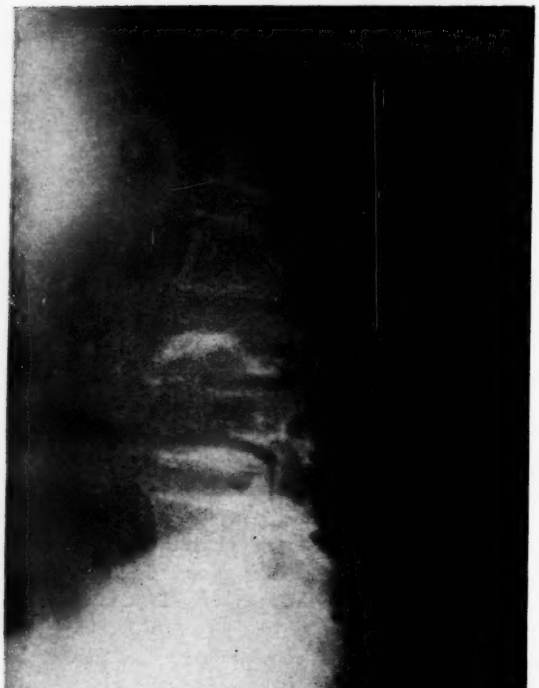

FIG. 16. Patient, age thirty-nine, with Cushing's disease due to bilateral adrenocortical hyperplasia. Lateral view of lumbar spine showing marked osteoporosis with collapse.

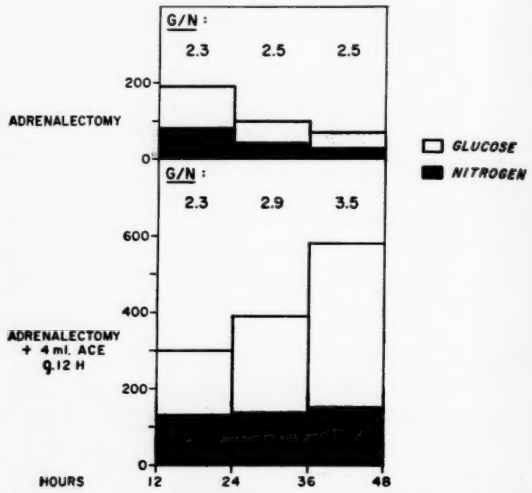

FIG. 17. Data from Lewis, Kuhlmann, Delbue, Koepf and Thorn.[65]

larly in the abdominal and interscapular region. This clinical observation not only suggests an effect of glucocorticoids on adipose tissue metabolism but suggests that adipose tissue in different areas of the body may respond differently to increased glucocorticoid activity. The anatomical specificity of adipose tissue is well exemplified by the unique response of total thickness skin graft from the abdomen to the arm and hand which, later in life, in conjunction with marked abdominal obesity exhibited a similar hypertrophy of the transplanted abdominal adipose tissue in its new environment.[52] Of course, increased appetite and total food intake frequently associated with Cushing's syndrome, as well as the compensatory insulin secretion which occurs in response to hyperglycemia, may alter the over-all glucocorticoid effect on both the quantity and distribution of adipose tissue.

Patients with Addison's disease are capable of forming ketone bodies and after an overnight fast the ketone level of the Addisonian may be somewhat higher than that of normal subjects. It is important to note, however, that this higher-than-normal blood ketone level is usually associated with a significant degree of hypoglycemia which is not present in the normal subject!

The administration of glucocorticoids to diabetic patients increases ketone production as well as blood and urinary glucose levels. Long and Lukens,[32] in 1934 and 1935, in carefully controlled studies in cats, established the beneficial effect of adrenalectomy on pancreatic diabetes and noted a concomitant reduction in blood and urine ketone levels. More recently, Scow[53] in adrenalectomized, totally depancreatized rats has demonstrated an extreme degree of ketonemia following the administration of cortisone, whereas no ketonemia was noted in the adrenalectomized-depancreatectomized untreated controls (figure 18). On the other hand, in the intact animal, Engel[54] has reported that glucocorticoid administration offers protection against ketosis. Consideration of the findings of Scow[53] and of Engel[54] suggests that in the intact animal glucocorticoid-induced increased production of glucose may stimulate insulin production which, in turn, inhibits ketogenesis. In contrast, in the pancreatectomized animal in which there can be no increased release of insulin, the ketogenic effect of cortisone is unmasked. Similar conclusions with regard to lipogenesis have been well documented by Hausberger[55]

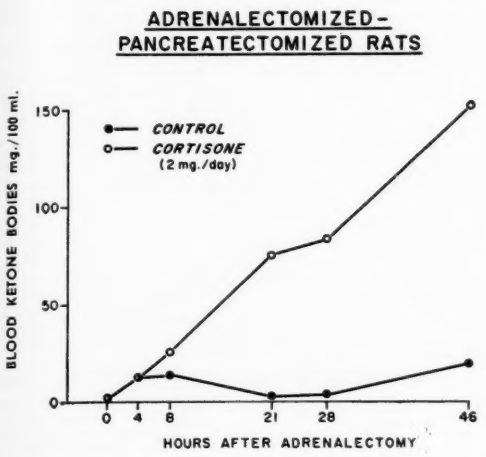

FIG. 18. Data of Scow.[53]

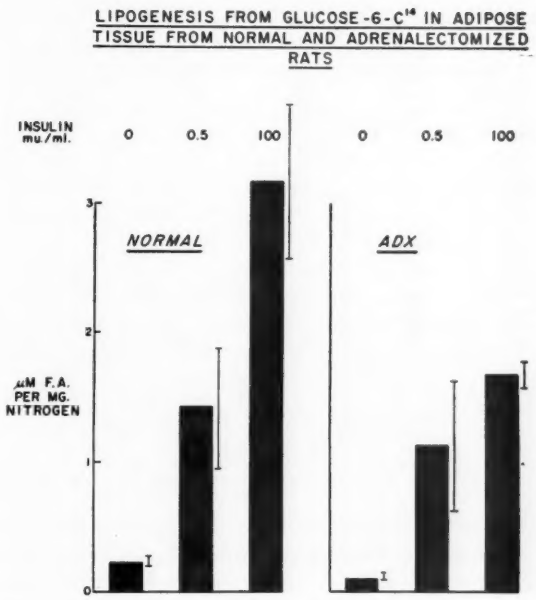

FIG. 19. Data of Jeanrenaud and Renold.[57]

in guinea pigs, and more generally reviewed by Bastenie.[50]

To date, in vitro experiments on adipose tissue carried out by Dr. Bernard Jeanrenaud[57] in our laboratory have failed to show a direct effect of glucocorticoids on adipose tissue as measured by fatty acid synthesis. Furthermore, adrenalectomy superimposed upon alloxan diabetes in rats does not restore depressed (diabetic) lipogenesis in adipose tissue as contrasted to the correction of the decreased lipogenesis in liver following adrenalectomy in a diabetic animal. Finally, adipose tissue obtained from adrenalectomized animals does not show an increased sensitivity to insulin as measured by fatty acid synthesis or CO_2 production (figure 19). However, recent experiments have indicated that there may be in this tissue a direct effect of glucocorticoids on fatty acid *release*.

THE ADRENAL CORTEX AND DIABETES MELLITUS

The most important problem in clinical management of diabetes concerns the etiology of the chronic vascular complications. Among the factors which have been considered are the adrenal cortical hormones.[58] In common with the majority of published studies, we have failed to find evidence of quantitative or qualitative dysfunction of the adrenal cortex in diabetes with and without late vascular complications. This is best illustrated by figure 20, which demonstrates both initial plasma corticosteroid levels and levels obtained after the intravenous administration of ACTH.[59] It is evident that significant differences between diabetic patients and normal subjects were not seen.

Similar findings have been reported by Jakobson[60] of Helsinki in an extensive survey of this subject.

In considering the experiments of nature it would seem that, although frank diabetes mellitus occurs in between 10 and 25 per cent of patients with Cushing's syndrome (figure 21), vascular complications of the diabetic type are not particularly prone to occur in this group. This observation may be a reflection of the short life span of these patients. Dr. Donald Beaven,[59] in our group, has recently reviewed the literature with regard to the simultaneous occurrence of diabetes mellitus and Addison's disease and it is of some interest that, as shown in figure 22, Addison's disease controlled with normal maintenance doses of cortisone does not prevent a significant number of patients with adrenal cortical deficiency from developing diabetes mellitus. Thus, although glucocorticoids are known to aggravate the diabetic state, it is evident that the diabetic state associated with Cushing's syndrome is not necessarily associated with severe vascular complications. On the other hand, Addison's disease does not seem to offer protection from the subsequent development of diabetes mellitus.

Further evidence against an important role of the adrenal steroids in the genesis of vascular changes in diabetic patients has been presented by Dr. Jørn Ditzel in his studies on the blood vessel changes in the bulbar conjunctiva of diabetics. In these studies the adminis-

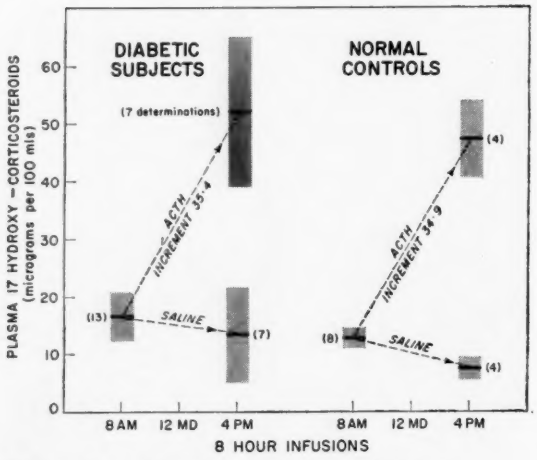

FIG. 20. Data of Ditzel, Beaven, Renold, and Thorn.[65]

tration of ACTH as an eight-hour infusion failed to aggravate the changes characteristically seen in diabetics or to prevent the diurnal involvement seen in this pattern during the reversible phase of this phenomenon.

Summary of glucocorticoid effects: The effects of glucocorticoids upon intermediary metabolism which have been considered are summarized in figure 23 in which primacy has been given to the increased catabolism of protein to amino acids, both in liver and extrahepatic tissues. However, it should be emphasized that such a summary is useful only in so far as it suggests important or critical experimentation. It may be of particular importance to point out that the known metabolic reactions in intermediate metabolism following glucocorticoid administration require between one and two hours in order to become apparent. Furthermore, recent studies with Cortisol labeled with carbon 14 have indicated that the onset and the peak of glucocorticoid action upon hepatic glycogen deposition, for example, occur at a time when Cortisol appears to have vanished from hepatic tissue.[61,62] Finally, it should be emphasized that each experiment has to be considered within the narrow context of the conditions prevailing in the organism or in the isolated tissue under which the experiment is carried out. Thus, Roberts[63] was able to show (figure 24) that glucocorticoids may enhance protein release by liver tissue under one set of conditions (normal rat liver slices), yet enhance protein synthesis by the liver under another set of conditions (after partial hepatectomy). If one considers the role of the adrenal cortex in facilitating the response of the organism to so many forms of biological stress, one may ask whether the major role of glucocorticoids in increasing the availability of amino acids in tissues and in plasma is not that of making available to all cells building blocks for intelligent metabolic adaptation.

Abnormalities of carbohydrate metabolism in forty-four patients with Cushing's syndrome

	Patients	Per cent
Abnormal GTT	33	75
Glucosuria	15	34
Fasting hyperglycemia	13	30
Overt diabetes mellitus	11	25

FIGURE 21

Coexisting diabetes mellitus and Addison's disease (1959)

	Number of cases
Addison's disease + diabetes	20
Diabetes + Addison's disease	37
Approximately simultaneous onset	5
Total	62

FIG. 22. As collected by Beaven, Nelson, Renold, and Thorn.[59]

Glucocorticoid effects on intermediary metabolism
A possible sequence

1. Increased amino acid production from protein (extrahepatic and hepatic).
2. Increased hepatic "trapping" of amino acids.
3. Increased transaminations.
4. Increased hepatic CO_2 fixation.
5. Increased hepatic fructose-1,6-phosphatase.
6. Increased hepatic glucose-6-phosphatase.
7. Increased blood glucose.
8. Increased blood lactate and pyruvate.
9. ? Altered extrahepatic glucose uptake and/or phosphorylation.
10. ? Altered lipolysis and ketogenesis.

FIGURE 23

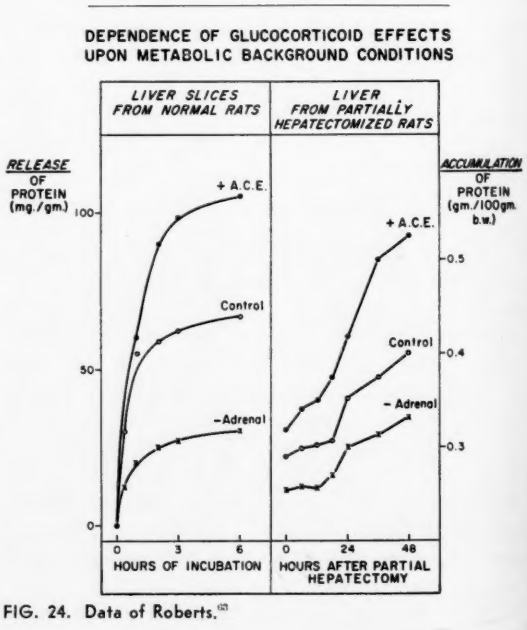

FIG. 24. Data of Roberts.[63]

CONCLUSION

The effects of epinephrine and hydrocortisone on intermediary metabolism have been reviewed and an attempt has been made to analyze the specific reactions responsible for the adrenal-induced diabetic-like state. The lack of evidence for the adrenal participation in the clinical picture of classical diabetes mellitus has been pointed out. The need for further extensive studies at the cellular level and in the intact animal and human patient are clearly evident. In closing, may I again express my appreciation to the Association for inviting me to present this Banting Memorial Lecture.

SUMMARIO IN INTERLINGUA

Le Corpores Suprarenal e Diabete: Interactiones e Interrelationes
Discurso Memorial Banting 1959

Le None Annual Discurso Memorial Banting esseva presentate per Dr. George W. Thorn de Boston le 6 de junio 1959, a Atlantic City, al occasion del Dece-None Assemblea Annual del Societate American pro Diabete.

Le thema del discurso es le effectos de epinephrina e hydrocortisona super le metabolismo intermediari de hydratos de carbon e le relation inter le mechanismo del action de iste hormones con le effectos de insulina. In conclusion le datos presentate es discutite ab le puncto de vista del rolo del corpores suprarenal in le historia natural de diabete mellite.

Le thema, assi circumscripte, representa un reporto partial de studios conducite per le autor e su gruppo de co-recercatores in recente annos con respecto a insulina e le steroides suprarenal in lor effecto super le metabolismo intermediari de hydratos de carbon e de grassia. Le serie complete de iste biologicamente activissime substantias es multo diverse con respecto al varie structuras chimic representate. Notante iste facto, le autor signala le correspondente multiplicitate de sitos e modos de action, justificante assi le restriction del presente reporto al supra-identificate thema special.

Le discussion de aspectos specific del thema es precedite per notas historic de character partialmente personal, visante a establir un specie de relation geographic e human inter le discopertas de insulina al universitate canadian de Toronto e de cortina (le non jam differentiate agente active del cortice suprarenal) al vicinissime universitate statounitese de Buffalo. Quando insulina esseva discoperite per Banting e Best a Toronto in 1921, solmente duo annos habeva passate depost le transferimento de Dr. Frank Hartman ab ille universitate a Buffalo ubi, in 1927, il esseva le gruppo de Hartman (nunc includente Dr. Carl Cori) que discoperiva cortina. Il esseva durante su association con Hartman e Cori a Buffalo que le autor del presente reporto disveloppava initialmente su interesse in le functiones metabolic de insulina e le steroides suprarenal. Pro clauder le circulo, il es a notar que Hartman habeva comenciate su carriera a Boston, al loco ubi le labores original includite in le presente reporto es in progresso.

Es presentate un revista historic de investigationes concernite con le rolo de epinephrina in le metabolismo de hydrato de carbon. Le contributiones de C. F. e G. T. Cori es sublineate. Le stato currente del cognoscentias relative a iste problema es summarisate sequentemente: Le action de epinephrina in musculo e hepate resulta in un intensification del activitate de phosphorylase e assi in un intensification del processo glycogenolytic. Secundarimente le accumulation de intermediarios phosphorylate—specificamente de glucosa-6-phosphato—inhibi le conversion de glucosa in glucosa-6-phosphato. Iste ultime phenomeno, in combination con le augmentate glycogenolyse e le augmentate rendimento de glucosa in le hepate, provide un explication pro le stato diabetoide que es inducite acutemente per epinephrina e que esseva reportate jam in 1901 per Blum qui usava pro illo le designation de diabete suprarenalin.

Es notate cursorimente le rolo de epinephrina in le metabolismo de histos adipose. Per contrasto con insulina (que effectua primarimente un augmento del synthese de lipidos), epinephrina promove le decomposition de lipidos e le liberation de acidos grasse e de glycerol a in le circulation. Iste effecto de epinephrina es analoge a su effecto glycogenolytic in musculo e hepate in le mobilisation de reservas de combustibile metabolic.

Le effectos de glucocorticoide (primarimente hydrocortisona) es discutite con respecto al gluconeogenese hepatic, al metabolismo de proteina, e al metabolismo de lipido. Un possibile sequentia del effectos glucocorticoide super le metabolismo intermediari es presentate. Illo consiste del sequente punctos: (1) Augmento del production de amino-acidos ab proteina (tanto extrahepatic como etiam hepatic); (2) augmento del "intrappation" hepatic de amino-acidos; (3) augmentate transaminationes; (4) augmentate fixation hepatic de CO_2; (5) augmento de fructosa-1,6-phosphatase hepatic; (6) augmento de glucosa-6-phosphatase hepatic; (7) augmento de glucosa sanguinee; (8) augmento de lactato e pyruvato in le sanguine; (9) possibilemente un alterate acceptation e/o phosphorylation de glucosa extrahepatic; e (10) possibilemente un alteration de lipolyse e cetogenese.

Le section concludente del reporto se occupa del relation del cortice suprarenal con diabete mellite qua entitate clinic. Es notate que le plus importante problema in le tractamento clinic de diabete concerne le etiologia de chronic complicationes vascular. Anormalitates in le function del hormones del cortice suprarenal es inter le factores que ha essite considerate como possibilemente implicate in le genese de ille complicationes, sed le autor del presente discurso reporta que nulle del varie studios interprendite per ille e su gruppo de co-recercatores ha producite evidentia de dysfunction quantitative o qualitative del cortice suprarenal como characteristica de diabete con o sin tardive complicationes vascular.

Iste observation se trova de accordo con le majoritate del studios del problema que ha essite publicate per altere autoritates.

Como quintessentia de omne su observationes le autor signala le urgente desiderato de extense studios additional, tanto al nivello cellular como etiam in intacte animales experimental e patientes human.

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Hypothalamic Control of the Anterior Hypophysis and its Metabolic Implications

Roger Guillemin, M.D., Ph.D., Houston

The importance of the anterior lobe of the pituitary gland in the establishment and course of diabetes mellitus suspected by clinicians for many years (see the review in 1938 by Atkinson on 817 cases of acromegaly) has been demonstrated by the now classical experiments of Houssay, Long, Lukens and Young. That this Society should be concerned with the relationships between "Brain and Diabetes" is most appropriate. There is now ample evidence that the functions of the anterior lobe of the pituitary gland are to a considerable extent dependent upon the integrity of its anatomical relationships with certain formations of the hypothalamus of the diencephalon.

Even though the hypothalamus is morphologically an ill-defined structure, anatomists recognize various areas* in the hypothalamus-pituitary complex particularly at the junction of hypophysial and hypothalamic tissues. These are the median eminence, the infundibular stem, and the infundibular process, all constituting the neurohypophysis or posterior pituitary. The pars tuberalis, the pars intermedia, and pars distalis all form the adenohypophysis or anterior hypophysis. The main body of the pituitary gland is connected to the hypothalamic structures in the floor of the third ventricle by the pituitary stalk.

Just as they have two different embryological origins, the two lobes of the pituitary also have two different types of connection with the hypothalamus.

The posterior pituitary gland is connected to the nuclei of the anterior hypothalamus (n. supra opticus, n. para ventricularis) and the nuclei of the tuber by a well-known tract of nerve fibers first described by Cajal and usually known as the hypothalamo-hypophysial tract. The two nuclei, supra opticus and para ventricularis, the hypothalamo-hypophysial tract and the posterior lobe of the pituitary are presently known to be concerned with the secretion of vasopressin and oxytocin.

The anterior pituitary is connected to the hypothalamus through an entirely different system. It is generally agreed that no secretory nerve fibers of hypothalamic origin similar to those of the hypothalamo-hypophysial tract are to be found in the adenohypophysis. An extremely well-developed and peculiar vascular system, however, connects the median eminence and anterior lobe of the pituitary gland. The original description by Popa and Fielding[2] of this portal system was later confirmed by Wislocki and King,[1] who furthermore concluded that blood flows in these vessels from their primary plexus toward the pituitary gland and that their secondary plexus irrigates the adenohypophysial parenchyma only. It was almost ten years later that Hinsey, and Green and Harris[2] suggested that this peculiar vascular formation might serve as a connecting link between the hypothalamus and the anterior lobe of the pituitary. The hypothalamic control of the functions of the anterior hypophysis would thus be of a humoral nature, the hypothalamo-hypophysial portal vessels serving as a carrier of the hypothetical mediators involved and liberated at the nerve endings which in the median eminence are in close relation to the capillary loops of the primary plexus.

The extent and the mechanism of the hypothalamic control of the anterior pituitary are still incompletely understood. That the anterior lobe of the hypophysis requires for a normal function the integrity of its connections with the hypothalamus has, however, been demonstrated in a variety of experimental circumstances. This short review will be mostly concerned with the secretion of ACTH, TSH and growth hormone, three hypophysial factors with important metabolic activities which are well known to the members of this audience.

*These various structures were defined and shown graphically by means of projection slides during presentation of the paper at the meeting of the Society. Since excellent reviews dealing with the anatomy of this region have recently appeared, the interested reader is referred to these.[1,2]

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Interruption of the stalk of the pituitary gland prevents the release of ACTH which follows exposure to certain stress situations. If a simple transection of the stalk is performed, the inhibition of the stress response first observed will, however, disappear and the normal pattern of ACTH release will be re-established. It is possible to correlate the return of normal functions with the regrowth of the portal vessels through the cut ends of the stalk. If the regeneration of the portal vessels is prevented, as by placement of a polyethylene sheath between the cut ends of the stalk, the blockage of the ACTH discharge will persist. It is interesting to note here that this blockage of ACTH release is not absolute and that some stimuli (laparotomy, traumatism, scalding, etc.) may still induce an apparently normal adrenocorticotrophic discharge. Also, after stalk section the adrenal cortex allegedly does not become as atrophic as it does following hypophysectomy. It would thus appear that a certain basal secretion of ACTH is still possible, at least for some time, in the denervated hypophysis.

Results very similar to these have been obtained after transplantation of the anterior lobe of the pituitary in areas distant from the hypothalamus. The growth of these animals with pituitary stalk section or peripheral pituitary grafts does not appear to be completely arrested; various authors have reported resumption of growth of the hypophysectomized animal after subcutaneous implantation of pituitary anterior lobes. Thus, the secretion of growth hormone may not require intact hypothalamo-pituitary connections. This question deserves further investigation in view of several reports somewhat at variance with these results.

The placement of minute lesions in various regions of the hypothalamus with the aid of a stereotaxic apparatus, a technic widely used recently in several laboratories, has also permitted localization of areas within the hypothalamus related to particular secretions of the anterior pituitary. Lesions in the anterior hypothalamus are usually followed by depression of thyroid function with maintenance of normal adrenocorticotrophic secretion. More posterior lesions or specific destruction of the median eminence have been reported to inhibit ACTH release in response to stress. According to McCann[5] the hypothalamic lesion which inhibits ACTH release always damages the hypothalamo-hypophysial tract, thus producing diabetes insipidus along with the ACTH-block. These questions should not be considered as satisfactorily settled. It is to be regretted that in most instances adequate histological control of the exact extent and localization of the lesions produced were not reported or performed; also, the recent introduction of more sensitive and more direct criteria of ACTH release (as compared to those used by these investigators) may make necessary a reappraisal of some aspects of these questions. For instance, in a recent series of experiments we have observed that minute lesions in the posterior hypothalamus may inhibit ACTH release without producing diabetes insipidus, and conversely that diabetes insipidus of considerable degree and several weeks' duration can be produced without interference with the release of ACTH.

Instead of localized stereotaxic lesions, functional inhibition of the normal activated state of the hypothalamus, as after administration of various pharmacological drugs (barbiturates, phenothiazine or reserpine derivatives), can inhibit the release of several pituitary hormones. Recent studies on the mechanism of these drugs have shown, furthermore, that their primary locus of action in inhibiting pituitary function may be at levels other than the hypothalamus (midbrain) even though their pituitary inhibitory actions are transhypothalamic. The integrity of various ponto-mesencephalic formations, parts of the reticular activating system, appears to be necessary for a normal hypothalamic control of pituitary release of ACTH and gonadotrophins. This concept has been strengthened by the results of electrical stimulations and of recordings of the electrical activity of various hypothalamic areas performed concurrently with endocrine studies.

The survival of fragments of pituitary tissue in vitro, with tissue culture or organ culture methods, has shown that the isolated hypophysial tissue ceases to secrete ACTH in the culture fluid within a few hours after explantation, although it will survive for months and differentiate its outgrowth into the classical type of pituitary cells. If, several weeks after placement of the pituitary tissue in culture, small fragments of ventral hypothalamus are introduced into the tube, ACTH activity reappears in the fluid. This was considered as suggestive evidence in favor of a hypothalamic control of the corticotrophic function of the pituitary.[3,4] It is interesting that injection of the fluids from these cultures to hypophysectomized animals did stimulate growth, disregarding age of the culture or absence of hypothalamic fragments. Here again, as mentioned earlier in the animal with pituitary stalk section or pituitary transplant, a fair degree of autonomy from the hypothalamus seems to characterize the secretion of growth hormone.

It would thus appear that the hypothalamic nuclei exert an important control over the function of the anterior lobe of the pituitary. The exact modalities and

the extent of this control are not definitely known. If intact hypothalamo-pituitary connections are necessary for adequate response of the pituitary to acute stimuli, some degree of pituitary autonomy is possible regarding ACTH and TSH secretion and to an even larger extent regarding growth hormone.

It was mentioned earlier, especially in view of the vascular connections existing between median eminence and anterior hypophysis, that a hypothalamic control of the pituitary should be neurohumoral in its ultimate effector. The results from the tissue culture experiments and the recent demonstration of an ACTH-releasing activity in the portal blood draining from the upper end of the cut pituitary stalk, have considerably strengthened this hypothesis. The only attempts made so far to identify the hypothetical mediators involved in the control of the secretion of the various pituitary hormones have been related to ACTH release. Using various in vitro technics as simple bio-assays, a corticotrophin releasing factor (CRF) of hypothalamic origin has been concentrated and partially purified.[4-6] It is none of the previously known neurohormones; it appears to be closely related by its physico-chemical characteristics to the small peptides of the posterior lobe of the pituitary. Recent studies have confirmed with in vivo technics the results previously obtained in vitro. The physiological significance of the factor isolated leaves little doubt, since it is highly active in stimulating release of ACTH in animals with a hypothalamic lesion which inhibits the ACTH secretion normally induced by exposure to stress.

The same material when administered intravenously to humans stimulates the release of ACTH as measured by levels of peripheral plasma 17-OH corticosteroids. Twenty-five to forty-five micrograms of the purified material given in one single intravenous injection elevate the plasma corticoids within a few minutes (figures 1 and 2).

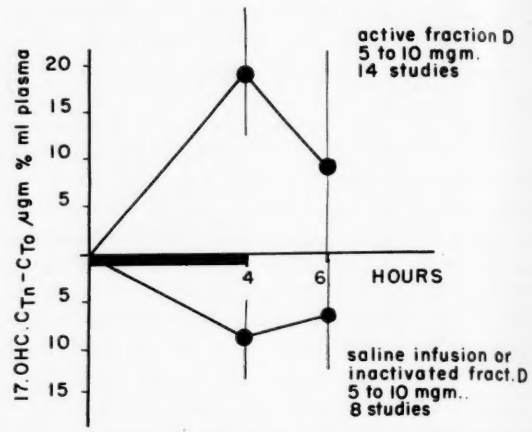

FIG. 1. Variations of the plasma 17 OH-corticosteroid concentration in normal individuals after a perfusion of the corticotrophin releasing factor (fraction D) purified on the basis of its activity in vitro. Bottom of diagram, control studies.

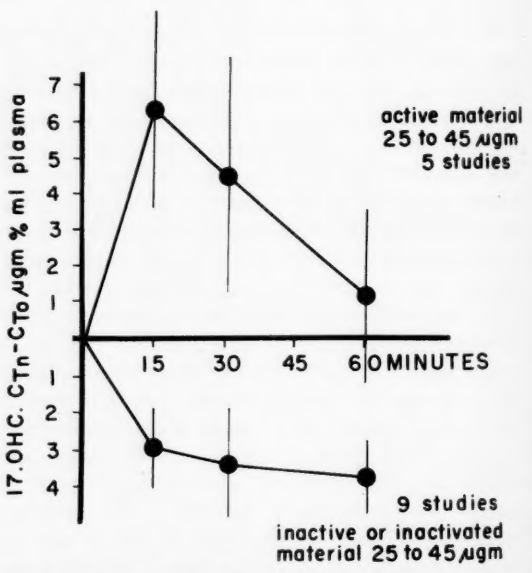

FIG. 2. Variations of the plasma 17 OH-corticosteroid concentration in normal individuals receiving a single intravenous injection of purified corticotrophin releasing factor (electrophoretic fraction DΔ). Bottom of diagram, control studies.

SUMMARY

The existence of a hypothalamic control of the anterior pituitary is thus well established. At a time when peripheral metabolic effects of purified pituitary hormones are being discovered, such as with corticotrophin and thyrotrophin, the metabolic implications of this diencephalic control are numerous. They may well encompass more than a simple transfer to the hypothalamus, of the hypophysial control of its various target glands.

Extensive investigations are still necessary to have a clear understanding of this problem. Of considerable interest also is the fact that this hypothalamic control of the anterior pituitary is humoral in nature. We have seen earlier that microgram quantities of a partially purified corticotrophin releasing factor injected into the human may influence considerably levels of pituitary adrenal function. We have preliminary evi-

dence that these metabolic factors of hypothalamic origin may be recovered in urine. Thus, in some not too distant future we may be able to study not only the pituitary but also possible diencephalic dysfunctions. It is even possible that we may be in a position to correct these dysfunctions by some replacement therapy, when we know more about the chemical structures of the neurohumors involved.

SUMMARIO IN INTERLINGUA

Le Governantia Hypothalamic del Hypophyse Anterior e le Inferentias Metabolic de Su Existentia

Le existentia de un governantia hypothalamic del hypophyse anterior es documentate e establite como facto foras de dubita.

A un tempore quando peripheric effectos metabolic de purificate hormones pituitari es discoperite progressivemente—per exemplo in le caso de corticotrophina e de thyrotrophina—le inferentias metabolic de un tal governantia diencephalic es numerose. Il es ben possibile que ille inferentias excede in lor signification un simple transferimento al hypothalamo del functiones governatori que le hypophyse possede pro varie glandulas dependente de illo.

Extense investigationes additional va esser necessari pro clarificar nostre comprension de iste problema. Un facto de interesse considerabile es que iste governantia hypothalamic del hypophyse anterior es de natura humoral. Nos ha vidite que microgrammas de un partialmente purificate factor liberatori de corticotrophina, quando injicite in subjectos human, pote exercer un influentia considerabile super le nivellos del function pituitari-suprarenal. Nos ha provas preliminari que iste factores metabolic de origine hypothalamic pote esser traciate in le urina. Assi il pare possibile que in un futuro non troppo distante nos va poter studiar non solmente dysfunction pituitari sed etiam le possibile dysfunction diencephalic. Il es mesmo possibile que nos va trovar medios pro corriger ille typo de dysfunction per le un o le altere therapia de reimplaciamento basate super nove cognoscentias del structuras chimic del neurohumores in question.

ACKNOWLEDGMENT

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DISCUSSION

LOUIS J. SOFFER, M.D.: I have had occasion to follow the work of Dr. Guillemin for a good many years, and in a much more modest way to attempt some studies in this area. I have been impressed with the results that he has obtained and the ingenuity of his experiments.

The problem is very interesting. In essence it revolves around whether the anterior hypophysis is stimulated to secrete its hormones essentially by fractions or agents originating somewhere in the brain or whether it is capable of being stimulated by some peripheral mechanism. The problem which has interested me primarily is the ability of the pituitary to elaborate corticotropin, and I shall confine my remarks to this aspect of the problem.

The first thing to bear in mind is that the adenohypophysis is a unique structure devoid of any neurosecretory fibers. We must assume therefore that in whatever way the anterior lobe of the pituitary is stimulated, it is via a humoral agent. This is the first concept that we have to accept.

In attempting to establish the nature and origin of this humoral agent, we are provided with some insight if we examine the anatomical nature of the blood supply to the adenohypophysis, and Dr. Guillemin has done this in detail. I would add one point and that is that in addition to the portal-hypophyseal system originating from the internal carotid artery and breaking up into capillaries in the region of the median eminence and then again collected in the form of a rather large blood vessel which goes to the adenohypophysis, there are branches which go directly from the internal carotid artery to the adenohypophysis, and not through the stalk or the hypophyseal system.

The implications of this observation are significant. They mean that the adenohypophysis is available for stimulation both by agents which find their way through vascular channels present in the hypothalamic area and by agents which reach the pituitary directly from the systemic circulation. In short, it seems to me that nature has been generous, and a variety of contingencies has been provided for.

The question then arises, are there any systemic agents and are there any agents originating within the hypothalamus which are capable of exercising an effect on the function of the adenohypophysis? There is the well-established concept that the secretion of the adenohypophysis, as far as ACTH is concerned, is influenced by the level of the circulating adrenocortical steroids. The mechanism of this effect is perhaps more debatable. The fact remains that as there occurs an increase in the circulating level of the glucogenic corticoids, there is a decrease in the secretion of corticotropin, and the antithesis is similarly true.

In the experimental animal, at least, the administration of epinephrine has resulted in a discharge of corticotropin from the adenohypophysis. This has been subject to some discussion, because although it could be demonstrated in the dog that following the administration of epinephrine, there is an increase in the plasma levels of the 17-hydroxycorticoids, similar observations have not been established in man.

It was suggested by Sayers that epinephrine acts by causing an increase in the utilization of the adrenocortical steroids and, therefore, an increase in the elaboration of ACTH.

In any event, the question arises whether the adenohypophysis is capable of reacting to epinephrine directly or whether epinephrine, if it exercises an effect on the adenohypophysis, does so essentially through the elaboration of the neurohormonal agent in the hypothalamus. The fact remains that in the experimental animal in which viable adenohypophysis is transferred to the anterior chamber of the eye, the local administration of small amounts of epinephrine resulted in an eosinopenia and lymphopenia. There is therefore some reasonably valid evidence to indicate that the adenohypophysis is capable of responding to an agent, systemically or locally introduced, as the case may be, without the intercession of the hypothalamus.

The next question that arises: Does the hypothalamus elaborate an adenohypophyseal stimulating agent? Dr. Guillemin has discussed this in detail.

I should like to describe again the nature of the experiments dealing with this problem, since they are interesting and the conclusions are based somewhat on what we conceive to be the merits or faults of this experimental approach. We have already discussed the portal hypophyseal system, and therefore it would seem very natural to introduce a barrier between the pituitary and the rest of the brain in an effort to determine whether the secretion of, say, corticotropin is thus interfered with.

When the stalk is sectioned, there occurs a decrease in the secretion of corticotropin, but it should be pointed out that the secretion of corticotropin does not cease and that indeed the experimental animal in which the stalk is sectioned is capable of responding to stress.

There is a question that arises in relation to this experiment. When the stalk is sectioned, the circulation of the adenohypophysis is interfered with. Therefore, is the decrease in adenohypophyseal secretion the result of the unavailability of a neurohumoral agent or is it due to necrosis of the pituitary resulting from the interruption of its blood supply?

I think that the stalk experiments raise as many questions as they answer. The stereotaxic experiments, perhaps, reveal some additional information. When minute areas of medial and posterior hypothalamus and the median eminence are destroyed, there is some evidence to indicate that there does occur an interference with the adenohypophyseal secretion of corticotropin. And, on the contrary, when these are stimulated, there is an increase in the secretion of this hormone. These results, too, although suggestive, are by no means entirely conclusive.

Perhaps the most rewarding experimental studies today are those of Dr. Guillemin and his group and Dr. Saffran and his co-workers. These have to do with efforts to isolate a fraction from the hypothalamus, which, in tissue culture of viable adenohypophyseal slices is capable of causing an increase in the secretion of ACTH.

In some earlier experiments by other investigators, explants of the posterior hypothalamus of the bull were capable of causing some increase in the secretion of ACTH, in contrast to those of the anterior hypothalamus, spleen and liver. These experiments, however, were crude and not entirely convincing.

Dr. Guillemin modestly passed over the nature of his experiments rather hurriedly, but I think it is worth while to examine them more closely. When one takes small areas of tissue or extracts of the medial or posterior hypothalamus, or of the median eminence, which are added to a culture medium containing vi-

able adenohypophyseal tissue, the resultant fluid when added to adrenal cortical slices causes an increase in the concentration of those steroid fractions which have a double bond between C_4 and C_5 and a ketone on C_3. We can conclude from the results of this experiment that there has occurred an increase in secretion of corticotropin by the adenohypophyseal tissue thus treated. Saffran and his group have similarly demonstrated that posterior pituitary extract and protopituitrin when added to adenohypophyseal tissue yield similar results.

These studies would therefore indicate that an agent or agents obtained from the medial and posterior hypothalamus, the median eminence and posterior pituitary extract are all capable of causing an increase in the secretion of ACTH by the adenohypophysis. When these various extracts were chromatographed, Dr. Guillemin found that one spot with identical R_f was common to all and which Dr. Guillemin referred to as compound D. When compound D, which proved to be a small polypeptid, was eluted it was found capable of causing secretion of corticotropin by adenohypophyseal tissue slices. This substance was effective in minute amounts varying from one to three gamma. This problem was further complicated by the fact that compound D was also present in a substance obtained from horse gut by Von Euler which he referred to as substance P. In any event an ACTH releasing agent is apparently elaborated by certain areas of the hypothalamus and perhaps even of the posterior pituitary lobe although the latter may simply serve only as a way station for the storage or transmission of this agent. In addition an apparently similar substance is secreted by horse intestine.

What are the conclusions that can be arrived at? It would appear to me that the available evidence suggests that the adenohypophysis can be stimulated to secrete corticotropin both by a neurohumoral agent having its origin probably in the posterior hypothalamus and surrounding area and by agents reaching it from the general circulation. Since the integrity of the adrenal cortex is essential for life such a dual control system would seem not unreasonable since a considerable degree of protection is thus provided.

I will conclude my remarks by expressing once more my appreciation to Dr. Guillemin and his co-workers for their most interesting and provocative studies.

DR. GUILLEMIN: I wish to thank Dr. Soffer for an interesting discussion of the experimental evidence on which are based the concepts which I presented earlier. The question of the possible ubiquity of the hypophysiotropic mediator, I did not intend to discuss here. I am glad, however, that Dr. Soffer introduced it in his discussion. Our studies indicated, indeed, that extrahypothalamic origins of the corticotropin releasing factor were perhaps to be considered. Teleologically it would make sense. The question is still with us and it is too early to answer it. The results obtained with a fraction of substance P mentioned by Dr. Soffer have to be confirmed in vivo. When composition and structure of the hypothalamic factor have been established, it should be easier to compare with it substances with hypophysiotropic activity and of extrahypothalamic origin.

In the Western world we are fortunate in being free from the worst enemy of expanding knowledge, authoritarianism, with which seekers after new knowledge have often had to fight. Nevertheless, it is in human nature to be allergic to new ideas, and discoveries are rarely received with undiluted enthusiasm. This is particularly true when the discovery impinges upon some vested interest or conflicts with the views of a scientific hierarchy. Many years ago T. H. Huxley pointed out that it is the common fate of knowledge to start as heresy and end as a superstition, and recognition that the end of this cycle has been reached is usually belated. Countless examples of opposition to new knowledge could be cited. This year has seen the centenary of the birth of Ronald Ross, whose discovery of the malaria parasite in the mosquito has had a decisive influence on human history. Yet, in the words of a recent appreciation, "at the time of his original discovery he received every possible discouragement from officialdom. He persisted in his work because he was a dedicated scientist." More appropriately today, we may recall that Addison's description of the disease which now bears his name was received with skepticism in many quarters and that reports of two or three cases presented to the London Medical and Chirurgical Society were refused publication in the *Transactions.*

A. S. Parkes, in "The Art of Scientific Discovery" from *Perspectives in Biology and Medicine* 1:377, Summer, 1958. Copyright 1958 by The University of Chicago.

Brain and Diabetes

The Role of the Highest Integrative Functions in Disease

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During the last quarter of the nineteenth century, it became increasingly evident to physiologists that the bodily responses of injured animals apparently experiencing pain often were indistinguishable from the behavior of frightened animals, who were neither injured nor in pain. Furthermore, after studying the secretory functions of the stomach, Pavlov was obliged to infer that these activities are so dependent upon the animal's reactions to conditions in the kennels and laboratories, before and during observation, that understanding of digestive secretion is impossible without evaluating the significance of these "conditions" to the animal. Such complexities could be avoided only by isolation of the part studied or by use of general anesthesia. Physiologists had to face the fact that, regardless of what functions might be exhibited in an isolated organ, in the intact animal all functions are influenced by central integrative action.

Naturalists, and more particularly zoologists, attempting to understand the behavior of living creatures, by preference and training observe them in their context. Looking at living creatures in their environment, naturalists have discerned not only their purposive patterns of behavior but also what have been called "displacement patterns"—the performance of a biologically inappropriate action when an appropriate one is blocked. The behavior does not serve directly the survival of the individual or the species. Biologically, it is irrelevant to the situation in which it is performed. For example, a wild rat that is feeding, when disturbed by another rat of a different species, makes aggressive noises and motions toward the interloper. The latter flees. But the first rat, instead of immediately resuming feeding, starts to groom its face with its forepaws, an action which it would not ordinarily perform in the middle of feeding. Deprived of the object of its aggression, the rat resorts to an alternative and inappropriate behavior pattern.

A man, when blocked in satisfying his needs, may similarly exhibit such displaced adaptive patterns. The capacity to exhibit such inappropriate reactions assumes dramatic significance to disease as an aspect of the mind-body relationship.

In the course of a lifetime several different patterns may be evoked in people who are threatened by numerous circumstances, or who only transiently achieve a suitable adaptation. Some persons, because of inborn or early acquired differences, feel threatened by circumstances which are not at all alarming to most people. In such cases ostensibly benign circumstances may evoke inappropriate responses.

If we now add to man's special needs his unusual capacity to react to symbols as though to significant events, it is evident that this capacity may enhance his ability to perceive threats as well as to increase his satisfactions. How, then, he perceives his immediate environment depends on his inborn equipment and early conditioning, as well as on a host of life experiences. Since pain or damage to tissue provokes vigorous general and local protective reactions, it can easily be seen that symbols of destructive experience can also evoke such reactions. This indeed they do, and often to a degree far more costly to the individual than the actual effects of the assaults they symbolize.

When a person's goals are defined and progress toward their achievement is satisfactory—without excessive conflict, postponement, or deprivation—the individual may be said to be in a phase of adequate adaptation.

When, for some reason, an individual feels himself to be seriously threatened and blocked in the pursuit of the fulfillment of his goals, he is said to be in a non-adapted phase. A conspicuous feature of this extremely precarious phase is an uneasy feeling—usually ill-defined—which is best described as anxiety. The person may also be aware that his thinking is not clear.

Since an individual does not necessarily recognize all of his goals, and since the goals themselves are often in conflict, and anxiety is at least transiently experi-

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enced by everyone, protective, defensive and compensatory reactions are widely seen. They help an individual both to avoid and to meet this nonadaptive phase, by carrying him through periods of environmental demands.

THE PROBLEM OF DISEASE

Claude Bernard, the great French biologist of the mid-nineteenth century, was among the first to see disease as the outcome of attempts at adaptation—attempts which, though appropriate in kind, are faulty in amount. Since the defensive response in its intensity can be more destructive than the original assault, an individual may be damaged gravely through the wrong magnitude of his defensive reactions. For instance, the presence of microorganisms in the lung calls forth cellular and humoral reactions that counter invasion, and do so effectively. Yet their magnitude may lead to congestion of the lungs and to pneumonia. This adaptive response becomes especially ominous for the individual when tissue is already involved in a longstanding overreaction as in chronic lung disease.

Because of the unity of mind and body, man reacts adaptively or defensively not only to damaging microbial and physical forces, but to threats and symbols of danger. Under circumstances perceived as threatening he may evoke inappropriately primitive metabolic or reproductive patterns that ordinarily serve to maintain the body and the stock. His adaptive and protective capacities are limited, and the form of the reaction depends more on the individual's nature and past experience than upon the particular noxious factor evoking it. Since certain bodily and behavior patterns are called upon to attain goals that can never be attained through their use, such inappropriate reactions are indefinitely protracted. Functions which are usually phasic become continuous. The tissues involved are thus pressed beyond their limits. In other words, devices that ordinarily serve to protect the body may destroy tissue. The evidence for this is now abundant.

At this juncture, important semantic difficulties warrant brief consideration. Phraseology such as "emotional causes of disease," "psychogenic," "psychosomatic," or "functional disease" are misleading since they imply a situation of "mind versus body," and fail to present mind-body as a unit, interacting with its environment. "Functional" disease as contrasted with "organic" implies that in the former no tissue damage has resulted from the attempt at adaptation and that the process is completely reversible. Neither is always true.

Over the years in studies having to do with disease, one organ, or system of organs after the other has been studied in people functioning in the context of their home and work environment.[1] For example, in a setting which the individual perceives as a threat of a certain type, the mucous membrane lining of the stomach becomes intensely engorged, its acid secretion greatly accelerated, and its rhythmic contractions augmented. This is the stomach pattern of a man preparing to eat a meal. Under circumstances that call for entirely different reactions of aggression or striking in anger, the individual inappropriately evokes an eating pattern. Similarly, the crying-out anger pattern, with hunger—one of the earliest to appear in infancy—may reassert itself in later life during periods of deprivation or repression of longings for emotional support. Since this displacement behavior seen in the eating patterns cannot satisfy such longings, the gastric activity is excessively prolonged and the lining of the stomach may digest itself. Peptic ulceration may ensue.

When a person is rejected or feels his prestige endangered, his glands of internal secretion may via central nervous system activity be induced to respond as though his very existence were in jeopardy, as by the sudden demands of low temperature or violent action.

ADAPTIVE REACTIONS AND DIABETES

Reaction patterns especially pertinent to starvation seem to be pertinent also to an understanding of diabetes mellitus.[2] These reaction patterns involve both the metabolism of fat and carbohydrates, and the urinary control of water and electrolyte excretion. An example taken from a recent experiment will illustrate this.

Earlier studies with diabetic subjects had indicated that when such people are exhibiting an endogenous glycosuria and when, under the stimulus of a threatening situation, they develop a diuresis, the concentration of glucose in their urine falls, although the rate of glucose excretion (mg./min./1.73 M.^{2}) rises.[3] The other aspects of the diuresis are the same as those exhibited in nondiabetic persons under similar circumstances, and are like that observed during starvation polyuria.[4]

Nineteen additional experiments have been carried out with nine diabetic subjects in my laboratories by Dr. Lawrence E. Hinkle, Jr., and his associates.[5] Thirteen of these experiments were "controls." There were six "stress" experiments, during three of which changes in urine flow occurred. One experiment will be outlined.

The patient, a middle-aged woman with mild diabetes, presented herself with a minor infection in one foot. This trivial injury had serious implications for the patient because her mother, also a diabetic, had had her leg amputated after what appeared to the patient to be the same kind of infection. Urine collection was

started as soon as she arrived. After a period of relative relaxation, she was examined by her physician, who took a noncommittal position, and with serious demeanor implied that the result of her urine output studies then being made would determine the subsequent steps to be taken about her leg. The patient thus remained in her seriously threatened, though silent, state for an hour. Thereafter she was reassured by being told that the foot disorder was of no consequence. The blood glucose concentration at intervals during the experiment did not rise, but fell slightly (table 1).

TABLE 1

Data from an experiment on a diabetic woman

	Time	Capillary blood glucose (mg. per cent)
	9:00	212.3
	10:00	210.2
	11:00	202.3
Threatening situation	12:00	202.3
	1:00	190.4
	3:00	183.5
	4:00	180.5

The diuresis that occurred in the setting of this threatening situation was manifested by an increase in the rate of excretion of water, sodium, and chloride, but no significant change in the excretion of any other solute except glucose (table 2). The rate of glucose excretion tripled during the diuresis, rising from 12.6 mg./min./1.73 M^2 to 35.8 mg./min./1.73 M^2. The glomerular filtration rate, as calculated from the rate of excretion of endogenous creatinine, did not change. The total osmolar load during the period of maximal diuresis was 0.75 mOsm./min./1.73 M^2. The obligatory excretion of water at this load is less than 1 cc./min./1.73 M^2, or more than twice as much water as was necessary to excrete all of the solute load, including glucose. Both before and after the diuretic period, the flow rate was no greater than that obligatory for the excretion of the osmolar load.

From these and other observations it has been inferred that a water diuresis occurred, and also that the increase in the excretion of glucose was not the result of an increase in the filtered load of glucose. This being true, the increased glucose excretion must have been the result of a diminution in the reabsorption of glucose by the tubules. This reabsorption is believed to take place entirely in the proximal tubule, and to involve a process of active transport by the tubular cells. The mechanisms by which this diminution in the reabsorption is accomplished are not clear. However, it is clear that adaptive reactions may produce an increase in glycosuria and polyuria in the diabetic through mechanisms involving the kidney directly, and that are not associated with an increase in the level of circulating glucose.

In these and other experiments most of the individuals who developed a diuresis appeared to be "anxious," "tense," "fearful," or "apprehensive," and most of them admitted to having some such emotion during the period of the diuresis. But not all did. An occasional individual appeared to be very little upset, and denied feeling anything unusual, although he developed a diuresis in clear temporal relation to a situation known to have threatening implications for him. On the other hand, a number of the experimental subjects looked disturbed, and reported that they felt anxious or apprehensive; but these showed no change in urine flow.

In other words, no inevitable connection between the diuresis and a specific emotion could be ascertained. Certain feelings such as anxiety or apprehension often occur as a part of the response of humans faced by threatening situations, and diuresis may also be a part of their response to such situations. The "emotion" and the diuresis are thus often linked, but they are not causally connected. It seems rather that both are a part of the total response of the organism to a challenge arousing feelings of anxiety or apprehension and im-

TABLE 2

Data from an experiment on a diabetic woman

	Time	Duration of collection period (min.)	Osmolarity (mOsm./L.)	Glucose concentration (per cent)	Total flow (cc.)	Rates of excretion (per minute per 1.73 M^2) Cl (microequiv.)	Na (microequiv.)	Glucose (mg.)
	8:40-9:30	50	795	2.56	0.4	48.3	45.3	10.2
	9:30-10:33	63	794	2.79	0.3	31.0	26.4	8.4
	10:33-11:30	57	739	2.52	0.5	60.4	51.5	12.6
Threatening situation	11:30-12:30	60	472	2.02	1.5	153.8	132.2	30.2
	12:30-1:30	60	342	1.63	2.2	170.9	152.8	35.8
	1:30-2:30	60	308	1.01	2.4	180.5	169.4	24.2
	2:30-3:37	67	583	1.67	0.6	67.6	55.5	10.0
	3:37-4:30	53	644	1.59	0.6	71.8	63.8	9.5

plying a need for mobilization for action. This diuresis characteristically occurs in what might be called "anticipatory" situations: in soldiers shortly before going into battle, in athletes shortly before participating in crucial contests, in students shortly before taking important examinations, in speakers shortly before mounting the rostrum, in passengers in an aircraft shortly before an instrument landing under difficult conditions. It subsides when the potential threat is either eliminated or defined. The diabetic woman, who had been led to believe that the results of the test in progress might be serious for her, no longer had a diuresis after the ominous implications had been dispelled.

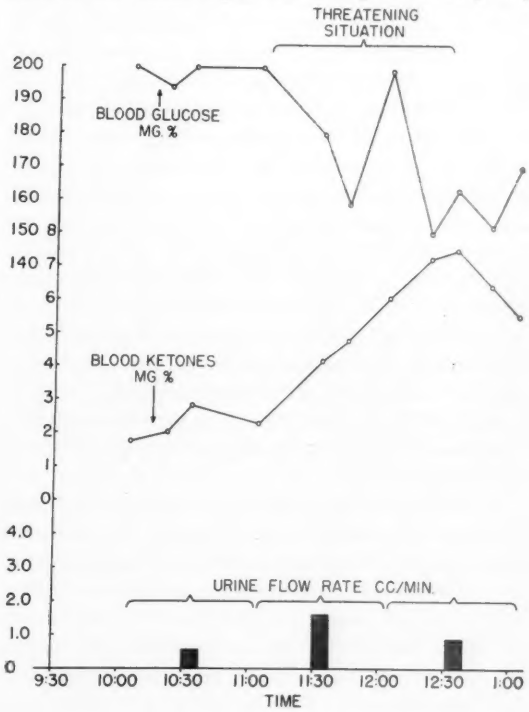
Reactions to experimentally contrived life situations like those in our laboratory experiments may be associated with a rise in the over-all metabolic rate, a relative increase in the utilization of fat, an increased breakdown of protein, and various evidences of adrenal-cortical activity.[6] Possibly some of these metabolic changes are either facilitated by, or result in, a loss of body water, and the associated diuresis may therefore have an adaptive value.

The phenomena here described have clear relevance to the management of the patient with diabetes mellitus. The labile diabetic, whose fluid homeostasis is maintained with difficulty, is vulnerable to such reactions. A "stress diuresis," occurring in a setting of acute interpersonal conflict, may be of great intensity and considerable duration, and the loss of fluid, fixed base, and glucose involved may be a potent factor in precipitating ketosis and dehydration. Rates of glucose excretion as high as 490 mg./min. (29.4 gm./hr.) have been produced experimentally during stress diuresis in fasting hydropenic diabetics. Diuretic responses have lasted as long as four hours, and have involved the loss of more than a liter of water, and as much as 102 gm. of glucose. When there is a large concentration of glucose in the urine, rates of excretion of chloride as high as 710 micro-equivalents per minute (42.6 milli-equivalents per hour) have been observed.

In other experiments made by Dr. Lawrence Hinkle it was possible to observe in response to threatening situations in both diabetic and nondiabetic persons a reaction pattern of increased ketonemia, increased fat metabolism, and a relative impairment of the ability to metabolize glucose. This pattern may occur in the absence of a significant change in urine flow (see figure opposite). Like the "stress diuresis," "stress ketonemia" often occurs in conjunction with lively emotional reactions, but these frequently are not the same as those associated with the diuretic reaction. Stress ketonemia often occurs in conjunction with moods of "sadness," "loneliness," "anger," and "resentment." It has been observed to occur during situations in which the individual has suffered the loss of a person or relationship that is important to him—for example upon receiving news of death, divorce, or desertion. It has also been observed during exacerbations of overt and furious conflict between parent and child and husband and wife. It is a metabolic reaction pattern like that observed during starvation or during strenuous and prolonged muscular exercise—marathon races, crew races, and football contests—where it has adaptive value in conserving glucose by increasing the relative proportion of fat consumed in the muscles. One may hazard the guess that it is a part of the organism's adaptation to food deprivation and extreme muscular activity and, like other primitive patterns cited above, it may be displaced or evoked inappropriately.

SUMMARY

The main point of this essay can be summarized as follows: As in the instance of stress diuresis in the diabetic patient described above, a bodily adaptive pattern integrated at a high level of brain activity but inappropriate to meet a crisis may be evoked even in the absence of significant disturbance in behavior, thought and mood. Signs and feelings of anxiety may



or may not be evident. Also, the various psychological defensive devices that act to achieve relative tranquillity in the face of threat may be inconspicuous, and the investigation of the patient with the aim of demonstrating striking psychological disturbances may be fruitless. Indeed, during a period of danger bodily adaptive processes, in some instances, would seem to act alone.

The stress that ensues within an individual as a mind-body unit from his complex interaction with his environment may end in disease and be relevant to the initiation and course of diabetes mellitus. This may occur through the initiation of inappropriate reactions and displacement patterns, besides other consequences of activity of the highest level of the nervous system.

The ecologically oriented physician is likely to perceive that a given setting, situation or relationship represents a serious threat to the patient. The less colorful day-to-day injuries, deprivations, frustrations, postponements, blocks to development and fulfillment, as well as the dramatic crises, then take on meaning and illuminate the initiation and course of disease. Such perception may lead him to constructive therapeutic acts.

SUMMARIO IN INTERLINGUA

Le Cerebro e Diabete: Le Rolo del Supreme Functiones Integrative in le Causation e le Curso del Maladia

Le these central del presente essayo pote esser summarisate sequentemente: Como exemplificate per le diurese post stress in le diabetico hic describite, un complexo de adaptation corporee—integrate a un alte nivello de activitate cerebral sed inadequate a stabilisar le dynamica de un crise particular—pote esser evocate mesmo in le absentia de un disturbation significative de comportamento, de pensar, o de emotivitate. Signos e sensationes de anxietate pote sed non debe esser evidente. In plus, etiam le varie mechanismos de defensa psychologic, que ha le objectivo de establir un tranquillitate relative in le presentia de un menacia, non es necessarimente conspicue; e un investigation del patiente, visante a demonstrar un frappante disturbation psychologic, produce possibilemente nulle resultato positive. De facto, il pare que in certe casos, durante un periodo de periculo, le processos de adaptation corporee age plus o minus in isolation.

Le stress que occurre intra le individuo como entitate psychosomatic producite per le complexe interaction del individuo con su ambiente resulta possibilemente in un stato pathologic, i.e., il es possibile que ille stress deveni significative con respecto al initiation e al curso clinic de diabete mellite. Isto pote occurrer in consequentia del initiation de inappropriate reactiones e complexos de displaciamento e in consequentia de altere effectos del activitate al nivello supreme del systema nervose.

Le medico qui es orientate ecologicamente percipe plus facilemente que su collega non assi orientate que un ambiente particular o un situation o un relation particular representa un serie menacia pro le patiente. Le micre adversitates del vita diurne—ille numerose e pauco grandiose injurias, privationes, frustrationes, retardos, e blocos de disveloppamento e satisfaction—si ben como le crises dramatic e evidente deveni alora significative in le interpretation del medico e pote illuminar le initiation e le curso de eventos pathologic. Le perception de iste aspectos del situation es frequentemente capace a suggerer al medico le selection appropriate de constructive mesuras therapeutic.

ACKNOWLEDGMENT

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DISCUSSION

ALBERT STUNKARD, M.D.: Dr. Wolff's paper is so rich and varied as to afford almost limitless topics for discussion. I would like to confine my remarks to one of these: the concept of emotion and its significance for a theory of disease.

Most writers in the field of stress and disease, the field of psychosomatic medicine, have grappled with the concept of emotion. And during the past thirty years almost every bodily disease has been ascribed to emotional determinants. Although the language has generally been more cautious in recent years, a great

many psychosomatic formulations still include emotions as causes of disease. Examples are the studies a few years ago ascribing gastrointestinal hypermotility to the effects of chronic anger. And to come closer to the theme of today's meeting, I might cite merely the title of another study conducted from this point of view, "The Influence of Emotions on Glucose Tolerance."

Such propositions relating emotions to bodily states were never verified. So the propositions were revised. Pathogenesis was attributed not to conscious emotions but rather to "unconscious" emotions. And both the presence of the emotion and the degree of its unconsciousness were cited as the pathogenic factor in the production of disease. One of the best known of these theories postulated that anger or hostility, repressed this time, causes essential hypertension. And a great deal of time and effort went into the attempt a few years back to show that only emotions which were repressed could really influence gastric activity.

Now if any of you have had difficulty in understanding how such immaterial entities as emotions were able to cause such material changes as hypertension, you were in good company. I doubt if even the people who advanced these theories had any clear idea how this could happen. For if we examine what is meant by the term emotion we find that we are confined to two rather limited kinds of meanings. One of these ways in which we talk about emotions is as feeling states, as, for example, when we speak of a throb of envy or a thrill of anticipation. In this sense of the word emotion, we are talking about events very much in the way that we speak about sensations. Indeed, when a person says that he has just felt a pang, we might very well wonder whether it was a pang of conscience or a pang of hunger. The term emotion in the sense of a feeling state is, thus, closely allied to the use of the term sensation, as a kind of self-diagnosis of certain physiological processes. But a diagnosis of a physiological process is far from being a cause of it. And the concept emotion, as feeling state, is clearly no adequate explanation of behavior, either of the whole person or of any of his various bodily parts.

There is another sense in which the term emotion is used, and it has come into vogue with the tendency to talk about unconscious emotions. This is the use of the word emotion in a dispositional sense, as a motive, as when we say "there goes a hostile man" or "here comes a mature man." We are clearly not saying anything about how the man feels. Indeed, much as we might wish it otherwise, the hostile man may be sitting on the top of the world and the mature man sunk in despair. When we speak of emotion in a dispositional sense we are making a statement about what these men are likely to do, given such and such circumstances. But the probability that a certain kind of behavior may occur in the future is hardly an explanation of bodily changes in the present.

From a purely formal point of view, then, it is unlikely that an emotion ever caused a bodily disease. However, as Dr. Wolff has said, upset people do become ill in a manner that seems related to their upset. How does he explain this?

He explains it, in the best scientific tradition, by locating the relevant variables in a verifiable, public universe of discourse. We hear, thus, in the first place, of threatening circumstances, and Dr. Wolff indicates how these circumstances can be defined, predicted, and even reproduced in a laboratory setting. We hear, in the second place, of the meaning of the threatening circumstances to the person, a meaning which can be defined for each person in terms of his constitution, his past experience, his present human relationships and his goals or aspirations. We hear not of specific pathogenic emotions, but of a nonspecific "nonadapted state." This third term in Dr. Wolff's framework appears to be both more inclusive and more clearly defined than any yet proposed for the description of the disturbed bodily homeostasis which occurs in situations of life stress. Those of us who have had the opportunity to review the dozens of behavioral tests which helped to define the "nonadapted state" have the impression that here, finally, we are dealing with public, verifiable statements about a great many issues which have been clouded in vague language about emotions and bodily disease. The fourth and final term in this framework is the "inappropriate adaptive response to stress" which resolves the "nonadapted state" and establishes that form of adaptation or nonadaptation which we call disease.

And how does Dr. Wolff use the term emotion? For Dr. Wolff emotion is a feeling state, which is one aspect of a failing adaptation to threatening circumstances. Clearly it is not a cause of the failing adaptation. For it is a report by the threatened person about the meaning of the circumstances which he finds threatening, and about the nature of his response to them. Here, finally, is a concept of emotion with which the physician can live in comfort and with profit. It implies no immaterial causes producing material effects. It does, though, help us to ascertain some of the circumstances which have determined our patients' illnesses and which define the possibilities of their recovery. For this contribution alone we are indebted to Harold Wolff.

Clinical Experience with Chlorpropamide in the Treatment of Diabetes

Garfield G. Duncan, M.D., Philadelphia

Oral therapy for diabetes is no longer a novelty. The apprehension concerning potential harm in the early stages of the treatment with the sulfonylurea compounds has decreased, but concern about the possibilities of accruing deleterious effects after continuous therapy for long periods remains, as might be the case with any new therapy. For the most part, reports on the effectiveness of these drugs deal with the many diabetic subjects who do not need drug therapy as well as the small percentage who do. This tends to foster rather than dissipate confusion. A grouping of the diabetic population according to their needs for, and likelihood of favorable response to, oral therapy indicates that:

1. Approximately 80 per cent of diabetic patients are overweight when they seek treatment for their diabetes. Control of the diabetes is readily achieved by reducing the caloric intake. Oral therapy is a needless but effective therapy for most of these patients. If employed it should be looked upon as a supplementary and temporary measure and one to be abandoned as soon as the weight reduction regimen maintains control of the diabetes. Unfortunately, the successful control of the diabetes by oral therapy in this segment of the diabetic subjects tends to detract from the importance of reduced caloric intake and, as a result, oral therapy and the overweight state are permitted to prevail. Indeed, the problem of obesity tends to increase.

2. Approximately 5 per cent of the diabetic population are juvenile diabetics in whom the oral therapy cannot replace insulin, hence is not indicated.

3. An additional 5 per cent at least is comprised of adults who have the juvenile type of diabetes, in which cases the sulfonylurea compounds also are ineffective. In effect, approximately 90 per cent of diabetics either do not need or do not respond to oral sulfonylurea compounds.

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Professor of Medicine, University of Pennsylvania and Director of Medical Divisions of the Pennsylvania Hospital and the Benjamin Franklin Clinic.

4. The remaining 10 per cent are adults who have the "adult acquired" stable form of diabetes but who are not overweight and who are, because of this nutritional state, deprived of the advantages that would accrue from an undernutrition regimen, and who require drug therapy —insulin or a sulfonylurea compound.

It would appear that this group—approximately 10 per cent of the diabetic population—is the ideal group upon which to observe most critically the effects of long-term sulfonylurea therapy. The temporary nature of satisfactory control of the diabetes with tolbutamide is most frequent in this group. In fact, in nearly one half of these patients in our series tolbutamide has gradually lost its effect after four to ten months of apparently satisfactory control of the diabetes. One such result has already been observed with chlorpropamide.

The foregoing grouping of diabetics, as summarized in table 1, offers a perspective from which to evaluate the clinical usefulness of the drugs under discussion. This report deals with a clinical testing of chlorpropamide in fifteen hospitalized patients with a follow-up of six months and a double-blind study of six weeks' duration with outpatients as subjects (similar studies using tolbutamide and carbutamide have been published elsewhere).[1]

TABLE 1

The relative and estimated frequency of four different groups of diabetic subjects and their relative sensitivities and apparent need for a drug therapy are indicated.

Nutritional state and type of diabetes	Estimated incidence in diabetic population (per cent)	Effect of sulfonylurea compounds
Overweight	80	Effective but not necessary
Juvenile	5	Ineffective
"Juvenile type" as seen in adults	5	Ineffective
Adult acquired diabetes in normal or underweight	10	Effective in more than one half of cases. Need drug therapy

Patients were hospitalized for a few days prior to the inpatient study, which consisted of a minimum of three consecutive five-day periods. During the first five days, the amount of insulin given was reduced or eliminated and in the case of patients receiving tolbutamide this drug was withdrawn. In each instance the object was to permit hyperglycemia and glycosuria to develop in order to discern more clearly the effect of chlorpropamide. During the second five-day period chlorpropamide was administered and throughout the third period this drug was omitted. Throughout the fifteen days, daily blood sugar determinations, by the Somogyi-Nelson method, were made on samples taken in the fasting state and at 3 p.m. with daily quantitative determinations of the glycosuria. Tests for acetonuria were done on successive voidings when the insulin therapy was reduced. Other laboratory studies were done during the first and toward the end of the second week. The diet remained constant throughout and undernutrition was guarded against.

In ten cases no acetonuria was detected during the first five-day control period, and in each instance chlorpropamide effectively controlled the glycosuria and hyperglycemia during the second five-day test period. In five cases either acetonuria occurred promptly, as illustrated in figure 1, or acute complications existed.

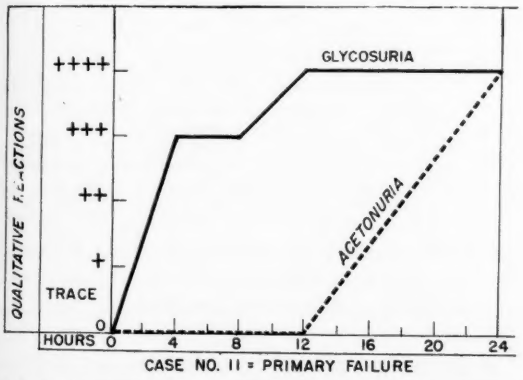


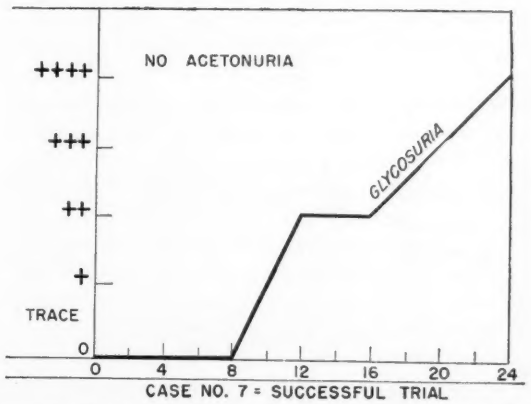
FIG. 1. Acetonuria as an indication of the probable effectiveness of a sulfonylurea compound: Case 11, the prompt appearance of acetonuria after the withdrawal of insulin, indicating that oral therapy will be ineffective; case 7, the absence of acetonuria after withdrawal of insulin provides a relatively reliable index that oral therapy will be effective (courtesy "Annals New York Academy of Sciences").[2]

In none of these was adequate control of the diabetes achieved with chlorpropamide and resumption of insulin therapy was necessary. One patient who prior to the test had been receiving 1.5 gm. of tolbutamide daily had fasting blood sugars ranging from 271 to 342 mg. per cent with an average of 296 mg. per cent. Chlorpropamide resulted in a prompt reduction of the fasting blood sugar to 82 mg. per cent. The comparative effects of tolbutamide and chlorpropamide, as observed during the period of hospitalization, indicate that chlorpropamide in this instance is a more potent blood sugar reducing agent than tolbutamide (table 2). This impression was supported by a follow-up of six months' duration, during which time 1 gm. of chlorpropamide was given daily and the fasting blood sugar values ranged from 147 to 210 mg. per cent with an average of 194 mg. per cent. The other patient, who had been taking 1.5 gm. tolbutamide daily for six months, had fasting blood sugar values ranging from 161 to 232 mg. per cent with an average of 184 mg. per cent. A prompt decrease in the fasting blood sugar to 84 mg. per cent ensued with chlorpropamide one dose of 1.5 gm. daily, and during the ensuing three months with a dosage of 0.5 gm. of chlorpropamide the fasting blood

TABLE 2

Comparative effects of identical doses of chlorpropamide and tolbutamide indicate that the latter is the more effective agent in reducing hyperglycemia (courtesy *Annals New York Academy of Sciences*)

	F.B.S.— mg. per cent	Average 3 p.m. blood sugar— mg. per cent	Urine sugar gm./24 hr.	Six-month follow-up average & range blood sugars, mg. per cent
Pretest control	228	284	9.8	
Chlorpropamide —1.0 gm.	147	168	2.1	194 (147-210)
Tolbutamide —1.0 gm.	184	262	11.3	296 (271-342)



sugar values have been normal, varying from 105 to 127 mg. per cent.

In two cases in which tolbutamide had been a recent secondary failure, excellent control of the diabetes was achieved with chlorpropamide.

Chlorpropamide had a blood sugar lowering effect in ten of the fifteen hospitalized patients. Following discharge from the hospital the diabetes in each of these ten patients has been controlled by 0.25 to 1.0 gm. of chlorpropamide daily. The average amount given in one dose daily was 0.75 gm. Experience with this drug and hypoglycemic reactions caused by it have prompted us to begin therapy with a daily dose of 0.5 gm. and modify it as needed. Additions of more than 0.25 gm. to the daily dose in one week increased the risk of hypoglycemic reactions.

Five primary failures with chlorpropamide therapy were noted. In two cases acetonuria appeared in increasing amounts in the first twenty-four hours after the withdrawal of insulin (figure 1). In another an acute cholecystitis with cholelithiasis was a complicating factor and in one metastatic carcinoma was present. One patient had gangrene of an extremity.

TABLE 3

A comparison of the effect of 0.5 gm. of chlorpropamide given twice daily with that when it was given as a single (1 gm.) dose indicates the greater uniformity of effectiveness in the latter (courtesy *Annals New York Academy of Sciences*)

Chlorpropamide	F.B.S. mg. per cent	Average 3 p.m. blood sugar mg. per cent	Urine sugar gm./24 hr.
0.5 gm., BID	108	242	2.8
1.0 gm., OD	147	168	2.1

ACUTE EFFECT OF A SINGLE DOSE OF CHLORPROPAMIDE

The speed of action, degree of effect and the duration of the blood sugar lowering effect of a single dose of chlorpropamide were observed when a liquid dietary formula, comprised of protein 113 gm., carbohydrate 268 gm. and fat 63 gm. (2,090 calories), was divided into twelve equal amounts, one of which was given every two hours throughout the twenty-four hours. As illustrated in figure 2, no hypoglycemic effect from 1 gm. of chlorpropamide was apparent in the first two hours, but an appreciable decrease in the level of the blood sugar had set in by four hours with a maximum blood sugar lowering effect at ten hours following

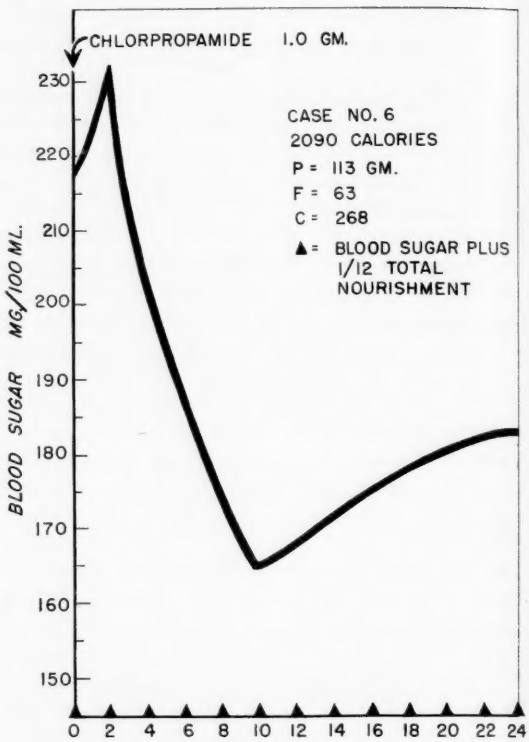


FIG. 2. The effects of 1.0 gm. of chlorpropamide in the case of a patient receiving identical nourishments at two-hour intervals indicate that: No apparent effect was exerted in the first two hours; a marked reduction in the blood sugar occurred between two and four hours; the greatest effect was apparent between eight and twelve hours, and the blood sugar lowering effect was still pronounced twelve hours after the dose was administered (courtesy "Annals New York Academy of Sciences").[2]

which a slow and very gradual increase began. A marked depressing effect on the level of the blood sugar was still manifest twenty-four hours after the drug had been administered.

A single dose of 1.0 gm. of chlorpropamide given with breakfast was more effective in preventing wide fluctuations in the blood sugar than when 0.5 gm. was given with breakfast and repeated at midday.

An outpatient study reported by Lee et al.[1] involved thirty-two patients in whom a double-blind study of the effects of chlorpropamide was completed. The trial was divided into three two-week periods of control, placebo and chlorpropamide administration. All patients were over forty years of age and the average duration of diabetes was seven years. Twenty-one patients had been treated with tolbutamide previously. In the trial,

twenty-five (78 per cent) of the patients had a fall in blood sugar of more than 20 per cent compared to control or placebo levels. During a follow-up period, all but three patients achieved excellent control with fasting blood sugar levels below 120 mg. per cent and aglycosuria. The maximum hypoglycemic response to chlorpropamide was often delayed until four to eight weeks of therapy, and a two-week trial is too short to determine the final degree of response in all patients. The average maintenance dosage with chlorpropamide was 0.5 gm. daily. Comparison of tolbutamide and chlorpropamide in the same patients frequently showed improved control with chlorpropamide. Hypoglycemic reactions, occasionally severe, were seen with doses of chlorpropamide over 0.5 gm. daily. Transient disturbance of hepatic function occurred in three patients and transient skin rashes in two cases. No severe drug reactions occurred which required treatment to be stopped.

SUMMARY

In summary, the study of the properties of chlorpropamide involving fifteen closely observed hospitalized patients indicates that: This drug is a potent blood sugar reducing agent when given in doses as small as 0.25 to 0.5 gm. per day; the blood sugar lowering effect becomes apparent between two and four hours after 1 gm. is administered by mouth and extends beyond twenty-four hours; after five days of therapy the hypoglycemic effect disappears gradually—over a period of three to five days after withdrawal of the drug; it served, with suitable dietary measures, to control the diabetes in ten of fifteen hospitalized patients having "adult acquired diabetes"; in no instance was it necessary, because of side effects, to discontinue the drug though one patient had a transitory macular skin eruption; there were no significant hematologic, renal or hepatic disorders attributable to this therapy; and the detection of acetonuria in increasing amounts after a reduction of the amount of insulin given served as a reliable guide in detecting those patients in whom a satisfactory response would not be obtained whereas, in cases in which no acetonuria occurred, there were satisfactory responses to chlorpropamide therapy.

In the study on outpatients chlorpropamide therapy reduced the blood sugar more than 20 per cent in each of thirty-two patients over forty years of age, and this drug was more effective than tolbutamide. Hypoglycemic reactions were not common in either of these studies, but they occurred for the most part in those patients taking chlorpropamide.

These and other studies indicate that at least two thirds of the adult overweight patients respond to sulfonylurea compound therapy and that chlorpropamide is a more potent blood sugar reducing agent than is tolbutamide. However, since they respond to dietary treatment alone, drug therapy is needless. Also, patients who are underweight or of normal weight and who have a stable form of diabetes and who need drug therapy, either insulin or a sulfonylurea, may respond favorably as indeed more than 50 per cent do. But, it is in this group that the favorable effect of the sulfonylurea compounds is most frequently temporary.

It would appear that these drugs, though quite effective in controlling diabetes in selected cases, are still on trial. Surveillance under close scrutiny for long periods is still necessary to prove the harmlessness of the sulfonylurea compounds. Also, the likelihood that such effective agents might receive widespread adoption as a substitute for appropriate dietary measures is a hazard to be guarded against.[2]

SUMMARIO IN INTERLINGUA

Experientias Clinic con Chlorpropamido in le Tractamento de Diabete

In summario, le studio del proprietates de chlorpropamido super le base de su uso in dece-cinque patientes hospitalisate e tenite sub stricte observation supporta le sequente constatationes: (1) Iste droga es un potente agente hypoglycemic jam in dosages de solmente 0,25 a 0,5 g per die; (2) le effecto hypoglycemic deveni apparente inter duo e quatro horas post le administration de 1 g per via oral e illo persiste durante plus que vintiquatro horas; (3) post cinque dies de therapia le effecto hypoglycemic dispare gradualmente in le curso de un periodo de inter tres e cinque dies post le discontinuation del droga; (4) le droga serviva—con le adjuta de appropriate mesuras dietari—a regular le diabete in dece ex un gruppo de dece-cinque patientes hospitalisate con "acquirite diabete adulte"; (5) il non esseva necessari in ulle caso discontinuar le droga a causa de effectos lateral, ben que un patiente habeva un transitori eruption macular cutanee; (6) il habeva nulle significative disordines hematologic, renal, o hepatic que esseva attribuibile a iste therapia; e (7) le detection de crescente nivellos de acetonuria post un reduction del dosage de insulina serviva como indicio secur pro le detection de ille patientes in qui un responsa satisfacente non esseva obtenibile, durante que in le casos in que nulle acetonuria occurreva, le responsas al therapia a chlorpropamido esseva satisfacente.

In le studio de patientes visitante, le therapia a chlorpropamido reduceva le nivello de sucro sanguinee

per plus que 20 pro cento in cata uno de trenta-duo patientes de plus que quaranta annos de etate; le droga se monstrava plus efficace que tolbutamido. Reactiones hypoglycemic non esseva commun in le un o le altere de iste duo studios, sed le reactiones occurreva le plus frequentemente in le patientes qui recipeva chlorpropamido.

Iste e altere studios indica que al minus duo tertios del adulte patientes obese responde a therapia a compositos de sulfonylurea e que chlorpropamido es un plus potente agente hypoglycemic que tolbutamido. Tamen, proque illes responde a dieta sol, le therapia a drogas non es necessari. Etiam multe patientes de peso normal o subnormal que ha un forma stabile de diabete e qui require un therapia a drogas responde ben. Isto vale pro plus que 50 pro cento de tal patientes. Tamen, il es in iste gruppo que le effecto favorabile del compositos de sulfonylurea es le plus frequentemente temporari.

Il parerea que iste drogas, in despecto de lor efficacia in regular casos seligite de diabete, es ancora experimental. Stricte observationes durante un longe periodo remane necessari pro provar le innocentia del compositos de sulfonurea. On debe etiam evitar le periculo que iste agentes, que es si efficace, es adoptate troppo generalmente como substituto de appropriate mesuras dietari.

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DISCUSSION

IRVING GRAEF, M.D.: The exact nature of diabetes still eludes us, and the attendance of many people from different parts of the country at meetings like this attests to the curiosity and the need for more information about various aspects of the disorder with which we are concerned.

I agree with everything Dr. Duncan has said with one exception. He stated that fears are subsiding about the use of these oral compounds. Speaking for myself, my fears are not subsiding. I keep hearing about misuse of the presently available oral compounds—accidents whether due to neglect or ignorance, some of which have led, unfortunately, to keto-acidosis and death in diabetic coma, or the opposite extreme, fatal hypoglycemia.

I hope that there are representatives of the advertising profession present in this room as I urge all of us to continue to use more insulin and less of the hypoglycemic agents than currently advertised.

There may be a real place for oral hypoglycemic compounds. Time and careful long-range studies will tell us what that place is to be. Dr. Duncan has already narrowed the group for optimal treatment to 8 per cent of recognized so-called "adult-onset" diabetics instead of 80 per cent as widely claimed.

The administration of potent oral agents that can produce a recognizable effect, using an index like the blood sugar or the content of sugar in the urine, is tempting when trying to help people control some part of their disorder so that they can lead "normal" lives.

The problem of the management of the ambulatory diabetic who is threatened by the effects of uncontrolled hyperglycemia, the threat of cataract, and retinopathy, and the threat of urinary tract infection, urges us all to continue to find a way to overcome the hyperglycemia.

But I suggest that the administration of an oral compound that lowers blood sugar to an overweight diabetic who has never exercised caloric restriction is to aggravate and abet his psychological as well as his physical disorders, even though it may achieve euglycemia.

There has been trouble with the administration of insulin from its introduction. We all know its abuse, too. The administration of insulin to fat nonketotic diabetic individuals likewise maintains the obesity and maintains the metabolic disposition towards diabetes, and it, too, should be withdrawn under proper circumstances. Excessive use may lead to unnecessary extra food intake with the inevitable gain in weight and the aggravation of the diabetic disorder. Dietary control in the vast majority of adult-onset diabetics combined with muscular exercise can control hyperglycemia and reduce glycosuria. Reliance on hypoglycemic agents, whether oral compounds or exogenous insulin, removes the emphasis from where it belongs—proper diet and exercise.

There is going to be no substitute for careful evaluation of each patient's therapeutic needs.

And again speaking for myself, I am not very much interested in the statistics of large numbers of patients who are given a common label which conceals the many variations among them.

There have been too many unqualified claims of therapeutic effectiveness of oral compounds in the management of the diabetes—a disorder which is exceedingly complicated and becomes more complicated as patients survive under the benevolent effects of insulin and antibiotics.

Sometimes I am tempted to try to write a paraphrase of Lewis Carroll's masterpiece and call it "Alice in Wonder Drug Land." I feel that we are so beset by claims of miraculous achievement by any number of agents for any number of purposes, I sometimes wonder whether or not I need to practice medicine thoughtfully or whether I can just open the daily newspaper or turn to the advertising pages of medical journals and share them with the patients, learning with them rather than being able to teach them.

The place of oral compounds might be defined better if we could adopt some sort of rules for their test and use. Dr. Duncan has already pointed out that in stressful situations, e.g., acute infections occurring in the tolbutamide-responsive patients, the drug loses its effectiveness, and the aware physician knows he must return to the use of the more dependable agent—insulin—for the control of the diabetic state.

If we are in agreement that the overweight diabetic should have no recourse to agents which will maintain obesity and merely keep diabetes latent, then it seems to me that our job in clinical testing is to find this group of 8 per cent of patients, who may be resident in the obese group once they are reduced in weight. We should seek to treat these people in appropriate therapeutic fashion with rigid scientific controls.

REED HARWOOD, M.D.: Dr. Duncan said we should restrict the use of tolbutamide to 8 per cent of our diabetics, and Dr. Stunkard tells us that we get a significant weight reduction in, at most, 30 per cent of the people whom we try to get to lose weight. I should like to ask Dr. Duncan what we should do with the fat diabetic in whom honest efforts to get control of the diabetes by weight reduction have failed. Isn't it better to get the blood sugar down to the proper level with the oral hypoglycemic agents or with insulin than it is to allow hyperglycemia to persist? Put another way, which is worse: an obese controlled diabetic, or an obese clinically uncontrolled diabetic?

HENRY E. MARKS, M.D.: I am concerned about chlorpropamide. We are on the threshold, apparently, of a much wider use of this very potent agent, and I should like Dr. Duncan's opinion about certain aspects which may have been minimized in his work because of restriction of maximum dosage to 250 mg. daily.

Although hypoglycemia, even severe hypoglycemia, can occur with tolbutamide, it is unusual and there is much greater danger of serious and prolonged hypoglycemic reactions with chlorpropamide. Likewise, there is much more danger of unrecognized hypoglycemic states, particularly when the optimal dose is not carefully determined by blood sugar studies.

The danger is the occurrence of serious hepatic toxicity. Since this is recognizable only by liver function tests we shall have to decide whether such studies should be done routinely on all patients receiving this drug.

MARTIN G. GOLDNER, M.D., (Chairman): In the beginning I raised the question of whether we had entered a new epoch in diabetic management. It seems that the tenor of the discussion favors an affirmative answer. The beginning of a new era is always characterized by a first phase of enthusiastic anticipation, and a second phase of equally enthusiastic rejection; then follows a leveling off of the emotions and a cool recognition of the facts.

Those who condemn the new drugs must not forget that they represent the first promising breaks in a search for oral hypoglycemic agents, which search has been longer than the search for insulin. The mechanism of the action of insulin is almost as unknown as is that of the oral drugs. In certain groups of diabetic patients, they effectively lower the hyperglycemia as well as the glycosuria. Since the disappearing glucose is not accounted for by glycogen deposition, it must be utilized for energy production!

The enthusiastic prophets of the new era will have to remember that the new drugs are no substitutes for insulin, that they may be used conveniently instead of the hormone in certain mild cases of diabetes, but that insulin is as essential as ever in combating diabetic emergencies, and in the treatment of juvenile, total, and severe diabetes.

Progress is achieved not easily; sometimes it is heralded when old tenets are cast in doubt and new ones are formulated. Nobody can doubt that we now find ourselves in such a phase in our thinking about diabetes. The unitarian concept of insulin deficiency is being replaced by one which considers a multiplicity of possible etiological factors. Among these are predominance of insulin antagonists, acceleration of insulin degradation and inhibition, changes in cell membranes, alterations in enzyme systems, etc. It is a logical sequela of these conceptual changes that hormone substitution may not be the only way of re-establishing normal carbohydrate metabolism.

The new drugs may not be the final answer to our problem but they are certainly one step ahead in our search for better understanding and probably also for better management of the disease.

DR. DUNCAN: Dr. Graef mentioned that I had stated

that fears of untoward effects for sulfonylurea therapy are subsiding. What I meant was that they appear to be subsiding, but I don't believe we are justified in having them subside until we have had a much longer and greater experience with them.

Dr. Hinkle asked me to outline the ideal circumstances in which it would be preferable to use the drug rather than insulin. In general, the ideal patient would be the one who must have a drug, either insulin or an oral preparation, and in whom we find that the oral preparation controls the diabetes. That will put the patient in the 8 per cent group.

An elderly patient who is blind or for some other reason may have great difficulty in the administration of insulin, would be another ideal candidate. I don't think that a blind obese person would be the proper candidate, though oral therapy would, no doubt, aid in controlling the diabetes.

It was intimated by one discussor that there is no evidence that the sulfonylurea compounds cause a reversal of the disturbed carbohydrate metabolism towards normal. But, we must agree that those patients in whom the drugs are satisfactorily effective do not lose large amounts of sugar as they formerly did. What happens to it? It must be incorporated into the body economy. And so, while all the questions are by no means answered and those doing basic research are troubled with some details that they have not been able to bring into line, I am quite sure that the carbohydrate that was not being metabolized before and was being lost is now being metabolized in those patients in whom the drugs are effective.

Dr. Harwood asked what one should do with a "fat diabetic failure." This problem haunts everyone who has a diabetes clinic.

Surely, it is an admission of defeat to give an oral preparation to a fat diabetic who won't adhere to a reducing diet. In our experience such patients who make no change from their faulty dietary habits become more obese as the result of oral therapy. Oral therapy in such cases intensifies the obese state as it controls the glycosuria.

We have been fortunate with some of these overweight patients by employing a plan that I have been using for the past three years for obese patients who would not reduce. We allow a 1300-calorie diet one day and 1600 the next, and continue to alternate the diets in this fashion over long periods. On the "low-calorie day" they look forward to the big feeding which they think the 1600-calorie diet really is. I have had success with this plan in treating patients who previously failed to reduce.

It is of prime importance, I think, to give these patients something they want to do more than they enjoy eating. If one can give them a motive, that is ideal and quite essential.

Dr. Knowles asked how to get the patients off tolbutamide. If they belong to the 8 per cent and the diabetes is well controlled, I would continue with it.

If they are doing well and are not overweight, then I would continue with this therapy. But if they are overweight, I would do my utmost to reduce their weight and then tell them, "You will need less of this drug and finally you will be able to give it up entirely and be on your own." It may be reduced from 1 gm. a day to half a gram as they lose weight, and finally the drug is omitted. This, I believe, is a justifiable plan by which oral therapy supplements *temporarily* the undernutrition therapy for patients who are overweight.

Dr. Weller mentioned DBI. I confess that I have had small experience with it. He stated that 55 per cent of a large series had no nausea. I interpret this to mean that 45 per cent experienced nausea. In the case of a drug that causes nausea, and possibly vomiting, in a juvenile diabetic to the degree of 45 per cent, I am quite prepared to let other investigators follow the clinical investigation of such a drug, because I don't think it will find widespread clinical application because the danger of its precipitating vomiting in children would be too great. This does not mean that in isolated cases it might not be quite satisfactory.

I agree with Dr. Goldner that a new preparation should only mark a new era when it is agreed by leading authorities that the new preparation is satisfactorily effective and harmless after long-term usage—i.e., years—and when its support is unanimous.

Special Article

Role of Environment and Personality in Management of the Difficult Patient with Diabetes Mellitus

Panel Discussion

Lawrence E. Hinkle, Jr., M.D., New York
Alfred Fischer, M.D., New York
Harvey C. Knowles, Jr., M.D., Cincinnati
Albert J. Stunkard, M.D., Philadelphia

DR. HINKLE (Chairman): The fact that the physician is unable to cure diabetes mellitus, but can nevertheless control it, places him in a peculiar relationship to his patient with diabetes. He and the patient have to cooperate with each other in setting up a regimen —sometimes fairly complex—and then they have to follow it for many years, tailoring it to meet the needs of changing conditions. This goes very well most of the time; for we all know that diabetes is a disorder not difficult to treat in most instances. But sometimes it goes very, very poorly, for both physician and patient. Under these circumstances we say we have a "difficult case," or a "difficult patient." It is these "difficult cases," or "difficult patients," that we wish to consider today.

From the point of view of the physician who treats diabetes, we have assumed that the difficult patient will fall into one of four categories:

1. He will be a patient who has an exceedingly labile form of the disease.
2. He will be a patient who exhibits behavior which makes his management difficult.
3. He will be a patient who cannot or will not follow a diet.
4. He will be a child with problems peculiar to the diabetic child.

I have invited several men who are especially well qualified to deal with these various points.

I shall ask Dr. Knowles to open this discussion, with a short consideration of the problem of lability, giving special attention to the extent to which the course of a patient may be influenced by the direct metabolic response of a man to his life situation.

Presented at the Symposium on Brain and Diabetes sponsored by The Clinical Society of the New York Diabetes Association, Inc., on Oct. 10, 1958.

DR. KNOWLES: My remarks today stem from observations in a juvenile diabetic clinic containing approximately a hundred teen-agers who are being managed with an unmeasured dietary regimen. It is the young diabetic who presents the most difficult problem in treatment today and who is particularly sensitive to environmental stress.

The unstable diabetic has three traits well known to all of you. First, his blood glucose concentration may fluctuate widely and rapidly without his knowledge of change. The fasting concentration may be 40 mg. per cent one morning, and 400 mg. per cent the next. Second, there is extreme sensitivity to small alterations in insulin dosage. For example, reduction of a daily dose of 40 units of NPH insulin to 36 units may produce that day not only glycosuria but polyuria. On the other hand, an increase to 44 units may well produce severe hypoglycemia that afternoon. Contrast this hypoglycemic response to that of a normal subject receiving intravenously 7 units of regular insulin in the course of an insulin tolerance test. His blood glucose concentration may decrease to 40 mg. per cent but he will feel little symptom of hypoglycemia, and his blood glucose concentration will have returned toward normal in an hour. Finally, the unstable diabetic often develops ketosis with alarming rapidity. In a period of eight hours the CO_2 content may decrease from 25 to 15 mM/L., with only moderate hyperglycemia.

In my experience the environmental stresses most commonly influencing carbohydrate metabolism in the unstable diabetic are starvation, exercise, events leading to excessive adrenalin secretion, infection, trauma, and emotional disturbance.

CHAIRMAN HINKLE: Dr. Knowles, to what extent do you think the direct metabolic response of the patient to his life situation influences lability? Does

this occur in rare, or in fairly frequent instances? Are the effects small, or of important magnitude?

DR. KNOWLES: To prepare for this panel I went over the immediate past three-year records of eighty patients to ascertain the incidence and reasons for deranged carbohydrate metabolism of degree sufficient to warrant immediate medical attention. There were eight patients who had hypoglycemia severe enough to require intravenous glucose. In six there were obvious physiologic reasons for the hypoglycemia. In the remaining two I could find no apparent reason, either organic or emotional.

Twelve developed ketosis warranting medical attention. Of these, five continued into acidosis. Comparison of the etiology of ketosis in this group with that in the adult stable diabetic reveals a decided difference between the groups. In two instances infection accounted for the ketosis, and in two others no apparent stress could be found. The remaining eight episodes seemed to be associated with emotional disturbance.

Of these, three patients omitted their insulin following family arguments, while five developed ketosis despite continued insulin and food input during what appeared to be emotional conflicts. A study of these conflicts would suggest that situations arose wherein the patient used his diabetes to assert himself, or that in contrasting circumstances, situations occurred threatening a patient who had spent his life in a very protective environment, usually fostered by an oversolicitous family. However, the exact relation between the environmental situation and ketogenesis is not wholly clear, since many patients with the personality traits described by Dunbar, Minsky, Alexander and others may retain good metabolic homeostasis despite extreme emotional conflict.

CHAIRMAN HINKLE: Dr. Knowles suggests to us that the adaptation of the diabetic to the people and events he encounters is of considerable importance in the management of his diabetes, especially if this diabetic happens to be a labile diabetic.

Dr. Stunkard, what, in your opinion, is the pathogenesis of overeating and obesity, and how would you go about treating it?

DR. STUNKARD: It is generally agreed that the most effective treatment for the middle-aged obese diabetic is weight reduction. Indeed, weight reduction is such an effective form of treatment as to raise the question of why any other form need even be considered, or why, indeed, the subject of the obese diabetic should appear on a panel dealing with "the difficult patient." The answers to these questions are surely no mystery to this audience. Weight reduction is a wonderfully effective form of treatment if only the obese diabetic loses weight. And this is the crux of the problem. Because by and large he won't lose weight. And on the chance that some of you may have thought that your difficulties with obese patients were due to some personal ineptitude, I thought that today I would give you some figures from a study which we have recently finished on the results of treatment for obesity.

The first part of this study was a review of the literature. By the time we had finished this review we were stunned, both by the number of papers that have appeared on the treatment of obesity and by the ineffectiveness of the results which they report. Literally hundreds of such papers have appeared in the past thirty years. Few, however, are of much help in evaluating the effectiveness of treatment. Most papers, for example, do not give figures on the outcome of treatment, and of those that do, most report them in such a way as to obscure results. Some authors, for example, report the total number of patients and total number of pounds lost without making clear how many patients achieved satisfactory results. Others report rates of weight loss of groups of patients for whom the duration of treatment was short or even unspecified. Perhaps the greatest difficulty in interpreting the results of weight reduction programs, however, is due to the exclusion from reports of patients who did not remain in treatment or were otherwise "uncooperative." In my experience such patients usually represent therapeutic failures, and they certainly constitute an impressive part of any group. Reports which exclude them, therefore, are not useful in evaluating treatment.

In our review of the literature we tried to include only reports that were based on the patients who started treatment, and only reports which specified the number of pounds lost by each patient during the weight reduction regimen.[1] We were able to find only eight such reports out of the vast literature on treatment.

There is no wholly satisfactory way of organizing and presenting the results of treatment, and we finally settled for a method which is at least easy to understand. This is to consider a weight loss of forty pounds as indicating considerable success, a weight loss of twenty pounds as moderate success and a weight loss of less than twenty pounds as no success. These are really pretty modest criteria when you consider that most of the patients in these series were from fifty to a hundred pounds overweight.

The results were all remarkably similar, and remarkably poor.[1] Six of the eight reports, for example, were

within seven percentage points of each other, and this remarkable uniformity, despite the widely differing circumstances of the studies, increased, we felt, the assurance with which the results can be regarded. As I have said, these were remarkably poor.

Only 25 per cent of the patients starting weight reduction regimens achieved the most success of a twenty-pound weight loss. And only 5 per cent were able to lose forty pounds.

These reports were written by persons with a special interest in obesity. Presumably they are more effective than the average physician. And this raised the question, "Could the results of routine treatment of obesity possibly be even worse than this?" To get an answer to this question we reviewed the results of treatment of one hundred consecutive obese patients who were referred to the Nutrition Clinic at the New York Hospital for weight reduction diets. These were one hundred unselected patients, referred from every clinic in the hospital, with the greatest number, probably, coming from the General Medical Clinic. After the prescription of the reducing diet the patients were seen at intervals of from two to six weeks in the Nutrition Clinic, and they also continued treatment for their original complaints in the clinic from which they had been referred. No drug therapy was administered in the Nutrition Clinic, but the entire medical armamentarium was, of course, available in the referring clinic. The lowest weight reached after the first Nutrition Clinic appointment was considered the therapeutic effect, even though the weight had subsequently increased.

The results of treatment in the Nutrition Clinic were even poorer than those reported in the literature. Only twelve of the one hundred patients succeeded in losing more than twenty pounds at any time during the treatment period, and only one of these was able to lose more than forty pounds. Furthermore, thirty-nine patients did not return to the Nutrition Clinic after their first visit, and, what is even more striking, twenty-eight never returned to any clinic of the hospital. Since admission to the Nutrition Clinic occurs entirely by referral from other clinics, this means the rupture of at least two therapeutic relationships.

I don't think that there is any need to go into the remarkably bad results of long-term follow-up of those few obese persons who are able to lose weight satisfactorily. I think it is clear why this relatively benign form of diabetes is such a problem, and why patients with this disorder merit consideration by a panel discussing the management of the difficult patient with diabetes mellitus. This is, of course, only to pose the problem. But at this stage of our understanding of obesity it may be more to the point to raise new questions than to attempt answers to the ones already asked. Or, to close with a lament by Archibald MacLeish,

"We know all the answers, the answers,
It is the questions we do not know."

CHAIRMAN HINKLE: Dr. Fischer, perhaps you can tell us what, in your opinion, are the problems and difficulties that the diabetic child encounters and how these may best be dealt with.

DR. FISCHER: Dr. Knowles started out by discussing the adolescent diabetic. I assume that these adolescents had been child diabetics, and therefore he saw them some time after I would be seeing them, and he had already inherited many of the problems which I was going to talk about.

From the moment that a physician diagnoses his young patient's disease as diabetes, he is faced with the problems and difficulties of the family and, very soon after, with those of the child himself.

Let us take the attitude of the family first. The realization that their offspring will always be a diabetic and will require incessant supervision places a great strain on the morale of the family. The ability to cope with the new situation varies tremendously with the education, emotional stability, economic security and strength of character of the parents. They may be overprotective, as shown by the mother who insists upon sleeping with her child for fear she will not detect an insulin reaction. On the other hand, the resentment against having to cope with a difficult situation leads parents to use insulin injections as a threat; for instance, suggesting an extra injection because the child "stole candy." The constant vigil, day in and day out; the supervision of diet and injections—all these strain the patience of most households.

The impact of diabetes on the younger child is purely physical at first. He has to be held for the injection, one or more times each day. It hurts; he cries and the parent is unable to explain to him the reason for it all. The child tends to get insulin reactions easily, which are often accompanied by behavior changes. He also learns to develop tantrums at will. Only last week one very young diabetic patient who was being scolded said, "I'll yell and scream until I get what I want." Often it is extremely difficult for a parent to tell when her child is really having a reaction or just a temper tantrum. Reactions can be lessened when quick-acting, short-duration insulin is used twice daily in young children, instead of a single dose of long-acting insulin.

The manifestations of hypoglycemic reactions change as the child grows older. Faintness, severe headaches or abdominal pain now become the most common symptoms. In older children, these reactions often affect schoolwork. By dividing the single dose of long-acting insulin ordinarily used into a morning and an evening dose, drowsiness and inattention in the classroom can usually be avoided.

Bed-wetting sometimes occurs as the result of polyuria and polydipsia early in diabetes. The child is often embarrassed by this symptom, which normally disappears after the diabetes is under control. But in some children the regression to the infantile state continues. The emphasis placed upon urinalysis at home may be one factor in the continuing enuresis.

I need not go into detail concerning the frustrating effects which diet restrictions have upon diabetic children, but I should like to mention the danger to the child of the uninformed and unintelligent parent who characterizes the occasional digression from the diet as "cheating or stealing." This harmful attitude produces a guilt reaction. The diet must be so planned that substitutions and extras are permitted.

On the question of diet restrictions, I am going to ask Dr. Knowles how he can manage a free diet and still avoid many insulin reactions without having a fairly stabile dietary regimen. In other words, I think one must draw the line here between strict diet and no diet. In other words, one can allow many exchanges of foods at various times of the day, whether it be this kind of carbohydrate or that kind of protein, but there must be some sort of schedule imposed upon the child and perhaps some limitation of excessive carbohydrate so as to have a balance between the insulin dosage and the diet.

Dr. Knowles touched on the problem of the growing diabetic child and the parents' unwillingness to permit their child to care for himself. Self-injection of insulin must be learned by the tenth year of age, if possible. This requires patience and understanding on the part of the parent and fortitude on the part of the child. Parents must learn to allow their child more freedom and independence. Excursions and overnight trips must be permitted as the child grows older. I have not the time here to stress sufficiently the advantages of summer camps for diabetic children. It is at such a camp that the child best learns that he can inject his own insulin. Moreover, the sharing of common problems for these growing boys and girls is a tremendous morale booster.

Problems change as the child becomes older. Most important is his increasing awareness of the so-called "stigma" of being a diabetic. All of us know the fear of every adolescent boy and girl of being different. The diabetic youngsters, especially the girls, often try to keep their condition a secret. The girls are afraid that their condition will keep the boys away and that they will be unable to attract a husband. Some girls have been married without telling their husbands of their disease. That there is need for frankness and honesty goes without saying. Psychiatric help is often needed.

In summary, I would like to say that, despite the handicaps, many children do well at school, at college, and in later life. The ones who have made the best adjustment are those who accepted their ailment as a condition and not a disease.

DR. KNOWLES: In reply to Dr. Fischer's question, our patients may well experience more reactions than those on a measured diet. I do not have available comparable data gathered from those on a prescribed diet regimen. I should say, however, that in our experimental study meals are eaten regularly, and the intake is frequently checked for quantity and quality with adjustments made when necessary. The difference from a prescribed regimen is that food isn't measured at mealtime. All unstable diabetics must have some regular pattern-of-eating habit or no satisfactory carbohydrate homeostasis can be achieved.

CHAIRMAN HINKLE: I think our audience is not going to let us get away without saying a few things about what can be done about the behavior problems of the diabetic; however difficult these may be, I shall try to meet this question head-on.

There are, as you know, more than a million people in the United States who have diabetes mellitus. There are at least that number who have some disturbance of mood, thought, or behavior—who have one of those illnesses generally called "psychotic," "psychoneurotic," "psychopathic," or who exhibit some other disturbance of their highest integrative functions. It is inevitable that these two categories of illness—the metabolic and the behavioral—should sometimes coincide. We know that people who have one type of illness are somewhat more likely to have another, and therefore it is probable that these two types of illness coincide somewhat more often than simple chance would lead one to expect. So, every now and then, one must anticipate that he will see a person with diabetes mellitus who also exhibits a disturbance of mood, thought, and behavior.

I think that I am safe in saying that there is no single pattern of mood, thought, behavior, or personality

structure which is always associated with diabetes. The only feature that always characterizes diabetes mellitus is an impairment of the ability to metabolize carbohydrate, and almost any sort of person can exhibit this. Yet it would be equally wrong to say that *no* disturbance of mood, thought and behavior is commonly associated with diabetes, for some are.

In the first place, many people with diabetes are somewhat discouraged at the time of onset of their illness. They are discouraged partly because they have the illness, but partly also because of the circumstances in which they find themselves at the time that the disease begins; for this disease is like many others in that it often becomes manifest at a time when a person finds himself coping with a difficult life situation.

In the second place, there can be no doubt about the fact that many people with diabetes have difficulty about eating. They find it hard to follow a diet, and this is exasperating to their physicians. But this should occasion no surprise to us—for, after all, hyperphagia is a cardinal symptom of the disease. Diabetes is an illness which classically occurs in obese people, who became obese because they had trouble in curbing their appetite. As Dr. Stunkard has pointed out, this disturbance of appetite has a very deep-seated basis. Since our treatment usually includes restricting the patient's food intake, we should not wonder if he has some difficulty in following the regimen that we prescribe.

And, as a matter of fact, the third phenomenon that one sees commonly in diabetic patients arises in part out of the very fact that we *do* prescribe a somewhat restrictive regimen for them, and then try to see that they follow it indefinitely. This regimen limits their food intake, which they find rather hard; it requires them to take injections of insulin, which most of them do not really like, no matter how much they may try to tolerate them; and it often sets them apart from their fellow men and restricts their activity in various ways. Lapses, lack of cooperation, and rebellion occur, especially in younger people and in those who are already rebellious by nature. Usually these episodes create family conflicts, especially in families where conflict exists already, and in many cases the physician is drawn into their conflicts when his own emotions and prejudices become involved.

Then, of course, on top of these problems common to many patients, there are the occasional patients who have disturbances of their mood, thought, and behavior, quite aside from the fact that they have diabetes.

How does the physician deal with these people? How can he avoid the difficulties that so often arise? For the purpose of emphasis I shall state flatly that the difficulties of physicians in dealing with these patients commonly arise from two defects on their own part: from a failure to maintain a proper attitude toward the patient and his symptoms, and from a failure to gather the necessary information upon which to base a course of action.

The professional attitude of the physician is well known to all of us. It is interested, sincere, and sympathetic, but at the same time it is detached and dispassionate. The good physician never ceases to be concerned about the welfare of his patient, but at the same time he never allows his emotions to becloud his judgment.

Most physicians maintain this attitude with considerable success as they deal with the bodily symptoms and physical disturbances of their patients, but many fail miserably when dealing with their patients' behavior. They are unable or unwilling to view disturbances of mood, thought, and behavior with a detached and clinical eye. All too often they regard these manifestations of the patient's illness—which, in truth, may be boundlessly annoying—as personal affronts, and as soon as their own emotions become involved they lose their effectiveness as physicians.

The second common failure is a failure to gather and organize the necessary information about the manifestations of the patient's illness and the circumstances under which it is occurring, so that a reasonably accurate working diagnosis can be arrived at and a course of management laid out. The physician always deals with the bodily symptoms and signs in this manner, carefully delineating the history and physical findings before proceeding to the diagnosis and treatment. The manifestations of the patient's mood, thought, and behavior, and their background, require similar treatment. Information about them must be sought, organized, and evaluated before treatment is undertaken.

A systematic consideration of the patient's state—what the psychiatrist often calls the "mental status"—is a first requisite: a consideration of his appearance, dress, behavior pattern, orientation, memory, thought processes (Is he hallucinated, deluded, paranoid perhaps? Does he have an aphasia?), his mood, his intellect, his insight, his judgment. In other words, the first step is to consider what manifestations of illness, if any, he has; for prognosis and treatment in this sphere just as in any other depend upon the nature of the syndrome.

The second step is to learn something about the

person in whom these symptoms are occurring, and the circumstances under which they have appeared. In other words, one needs to know about the patient's background and his present life situation. This one obtains in a very simple manner: One simply asks the patient. After all, he came to a physician, and he expects to be asked questions. Naturally, if one asks him, does he love his mother? or, does he get along with his wife? the answer will be "yes." But if one asks him who he is, where he came from, and what has happened to him recently, he is very likely to answer promptly and correctly. Here, again, simple, organized information is needed: What is his ethnic background, his geographical origin? From what segment of society does he originate? What is his life history, and what is his present life situation? Who were his parents? Where did they live? What did they do? Where was he born? How many brothers and sisters had he? What happened to him in childhood? And so on, right down to the present.

An experienced physician can obtain the rudiments of the whole history in a half hour.

One does not obtain all of this information simply for idle curiosity. One uses it in order to plan the management of the patient, which is dependent upon the information that one obtains.

CHAIRMAN HINKLE: Dr. Stunkard, do you agree with this or am I stating it too firmly?

DR. STUNKARD: Well, I think I would agree with the sense of your remarks. As I understand it, you outlined two difficulties which may lead to a less than optimal relationship between the physician and his patient. The first of these is when the physician personalizes all sorts of things which need not be personalized, when he loses his professional attitude, what has been described as his attitude of detached concern. I think that is a good description of the professional attitude—detached concern. The second kind of difficulty—which may be closely related to the first—is when he fails to obtain enough information upon which to base a plan of treatment. And such information is certainly a lot broader than the purely pathological, or pathophysiological.

CHAIRMAN HINKLE: Dr. Fischer, could you say a word about these problems?

DR. FISCHER: I was thinking, while Dr. Stunkard spoke, that perhaps all diabetic children and their parents might be better off if they had some psychiatric help right from the start.

We have tried to do this with the help of a psychiatric social worker who sometimes visits the family at home. This is done through our outpatient department at the hospital in conjunction with welfare services.

In private practice it is not as easy to do that. It is up to the physician himself to take enough time and go over various points which arise. But of course, there is a limit to the amount of time that one can give to a certain job each day. It is here that additional guidance may have to be offered in the form of psychiatry or family counseling.

I wonder if I could also say something about insulin's effect on the brain. Some years ago we worked intensively on the effects of insulin, in the crude way of the clinician, on diabetic children's psyches. We did serial I.Q.'s over a number of years and found that those children who had frequent insulin reactions did not vary very much from those who had few.

We attempted to find out whether because every diabetic child has some hypoglycemia daily, or perhaps each week, there was any effect on his mental state. We could not detect any.

At the same time we did extensive electroencephalographic studies with Dr. Hans Strauss, and noted very interesting changes when the blood sugar was low. There were marked changes in the EEG, which the administration of a small amount of glucose would immediately correct. Some of our patients did have more or less permanent changes, regardless of the blood glucose level, but when we repeated the EEG's—and this is why the paper was not published—some of the changes which were rather constant in children and which were considered as evidence of brain damage disappeared when they became adolescent. So I am glad we never published the paper, because as far as the EEG's were concerned, subsequent graphs showed a normal pattern.

CHAIRMAN HINKLE: I should like to comment on the use of psychometric tests as evaluators of disturbances of the highest integrative functions.

If I were to stand before this audience and say that I had estimated the blood urea nitrogen of fifteen people and had found all of them to be within the range of normal, and I concluded from this that each of these people had an entirely normal metabolism, I should be laughed out of court. The use of a single chemical test as a measure of the total metabolism is patently absurd. However, many physicians do not realize that tests of the highest integrative functions are not only more limited but cruder than most of our clinical laboratory tests. Furthermore, sometimes the tests that we rely upon most, or think of as being the most valid, often are the least sensitive and the most

dependent upon clinical judgment. To say that a person is "normal" because he performs "normally" in a single psychological test, or even on several, is quite misleading.

My second point concerns the electroencephalogram. If you take measurements on people with known amounts of brain damage, you will find that there can be marked disturbances of a man's ability to deal with his life situation long before he shows any significant disturbances of his EEG. As a matter of fact, a man may even show a marked falling off in performance on some psychological tests before his EEG becomes clearly abnormal.

With regard to the form that the history should take, I think Dr. Stunkard and I are really not very far apart; however, I would say again that I feel that in psychiatric diagnosis there is a very definite advantage in knowing what information you want and in going about getting it in an organized manner, just as this is advantageous in the area of physical diagnosis. I believe that we need an organized body of information, and I lean more toward direct, straightforward history taking, and the evaluation of the biography and the clinical manifestations of the individual, and less toward the more diffuse and free-flowing information gathering that has been in the psychiatric vogue for some time.

Dr. Knowles, do you have any comments at this point?

DR. KNOWLES: No, I think I agree with what has been said in general.

CHAIRMAN HINKLE: We have some questions now.

"One of the most common and difficult problems we face is that of food addiction, both in the genesis of diabetes and in its treatment. Are there physiological factors involved in this mechanism or is it all psychological? What is its relation to alcohol addiction and addiction to narcotics?"

Dr. Stunkard!

DR. STUNKARD: That is a good question, because these terms "food addiction" and "compulsive eating" are widely used and widely misunderstood. Let's take first—"food addiction." I just don't think such a term is justified in terms of what we know about addiction to alcohol and drugs. The main features of such addiction are the administration of a substance with specific action on the brain, habituation to the effects of this substance and withdrawal symptoms when it is discontinued. None of these features is present in the overeating of the obese person, and I think that this admittedly colorful analogy only serves to obscure our imperfect view of the problem.

Now as to the term "compulsive eating." In contrast to the concept of "food addiction," such a term seems fully justified. In current usage a compulsion is viewed as an irresistible urge to perform an apparently unreasonable act. Furthermore, it is inferred that the compulsion arises as a result of the displacement of a conflict from one area to another, thus defending the person against anxiety. Now in terms of what we know about so-called compulsive eating, both of these considerations hold. Some obese persons view their overeating as due to irresistible urges. And in three or four individuals I have met it has seemed to me that their outbursts of overeating resulted from a displacement of hostile impulses originally directed towards persons in their environment. So both the formal qualities as well as the psychodynamic backgrounds of their eating have all the characteristics of a compulsion. One further characteristic—all of the people I have seen whose eating I would consider as truly compulsive have overeaten in a pattern which is remarkably like that of an alcoholic's "binges." That is, they have relatively short outbursts of frantic gorging followed by periods of depression and remorse. I would like to end this talk of compulsive eating by saying that very few of the obese persons I have studied have shown this kind of overeating. My guess is that it is a rather rare phenomenon, and not one of great practical importance in the over-all picture of obesity.

CHAIRMAN HINKLE: Do you think that the obese people have a greater appetite or do they have greater difficulty in curbing their eating? Is appetite the problem?

DR. STUNKARD: Well, this gets into the question of whether it is a hunger drive or the failure to shut off a hunger drive that is involved in overeating. In certain forms of experimental obesity in animals there is no increase in hunger, or appetite, or drive to eat, as measured by the usual experimental psychological methods of measuring drive. In other words, the animal won't work any harder to get food; but once the food is available, for some reason the obese animal just keeps on eating and doesn't stop.[2]

I think that something analogous to this may be going on in some obese people. You get the impression that they are never really voraciously hungry, but if there is food around, they just keep on nibbling.

Another question comes up as to the total amount of food that obese people eat. Probably they eat more than thin people, because their basal metabolic requirements are so high. But there is some evidence beginning to come in that obese people are unusually inactive, physically inactive. As a result their total caloric

intake may actually not be any higher than that of lean people and their caloric surplus may result from a lesser energy expenditure.[3]

CHAIRMAN HINKLE: Dr. Fischer, I have a question for you. "Does tolbutamide have any place in the management of a juvenile diabetic?"

DR. FISCHER: No, but I would like to qualify the statement. I suppose that in the beginning—well, let's go back to 1923, when insulin first came out—there were still some children alive who survived one or two years without insulin. Today if one treats a diabetic child with insulin for a short period of time, it may be possible to get him sugar-free and withdraw his insulin. This can be done particularly in the summer, when there is activity and no infection around. On a fairly good diet, let's say, he will get along without any glycosuria. What he will not do is gain weight. One of the functions which we must provide for in a diabetic child is normal growth. This he does not get until you start to give him insulin again. Then he will metabolize just enough extra carbohydrate to gain height and add weight. If you put him on tolbutamide at the time when he was not on insulin, he would do no better than if he were receiving no insulin.

CHAIRMAN HINKLE: The questioner is especially interested to know whether you could use one of the oral hypoglycemics in an adolescent who refused to take insulin and resisted treatment.

DR. FISCHER: I have not had that experience. Dr. Knowles can probably answer that. My guess would be that it would be the same as in the diabetic child.

DR. KNOWLES: My reply echoes that of Dr. Fischer. The adolescent diabetic will not respond satisfactorily to the currently used oral hypoglycemic agents. If he refuses to take insulin, he will soon become ill enough to seek proper therapy.

CHAIRMAN HINKLE: I think we are going to have to close the panel unless there are one or two urgent questions from the floor.

DR. MARTIN G. GOLDNER: I suppose that we are all as disappointed as Dr. Stunkard is about the poor results of weight reduction programs. I wonder, however, if the experiences are not generally better in the treatment of the obese diabetic or the obese cardiac, i.e., with patients who have some specific reason and rather strong motivation to reduce weight. This, at least, seems to me to be so and I would like to ask Dr. Stunkard whether he has data on such selected groups of obese patients?

DR. STUNKARD: Actually, the only report on that is the one by Osserman and Dolger which came out about ten or fifteen years ago from Mt. Sinai.[4] Their results were about the same as those of others. I think 29 per cent of their patients were able to lose twenty pounds and 2 per cent lost forty pounds.

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It is impossible to understand the detailed mechanism of the mode of action of any pharmacologically active substance on the basis of its effects in the intact animal; conditions are far too complex.

Progress towards the elucidation of the mode of action of pharmacologically active substances is made when their effect can be reproduced in isolated organs, tissue slices or tissue homogenates; it then becomes sometimes possible to localize the drug effect on definite enzyme systems. Several of the vitamins have in this way been recognized as essential components of enzyme systems, for instance vitamin B_1 as cocarboxylase and vitamin B_6 as the coenzyme for transamination. No such success has as yet been attained in the case of the hormones, which may be due to the fact that their action is bound up with the structural organization of the cell. However, clear-cut in vitro effects on isolated tissue or tissue slices have been obtained with several hormones, and insulin was the first hormone for which such an effect was firmly established.

E. B. Chain, A. Beloff-Chain, and F. Pocchiari, from "Present Knowledge of the Mechanism of the Mode of Action of Insulin," in *Selected Scientific Papers from the Istituto Superiore di Sanità*, Vol. 1, part 3, p. 409, 1956.

Self-destructive Behavior in Young Patients with Diabetes Mellitus

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Certain irrational, peculiar, or unintelligible behavior in young diabetic patients may best be understood as essentially self-destructive. Such behavior includes the purposeful omission of food or overdosage of insulin to produce hypoglycemia; the omission of insulin and the neglect of a serious complication so that acidosis results; misuses of diet and insulin as weapons directed against the self as well as against the environment; and uncommonly, suicide through the agency of diabetes or by some other means.

These patterns of behavior may be carried out unconsciously or may be associated with a considerable degree of awareness. They may, indeed, constitute the principal forms of behavior by which the young diabetic interacts with his total environment and are consequently of greatest importance to recognize and understand. Some variations of this type of behavior are illustrated by the following four case abstracts.

CASE REPORTS

Case 1, J.L. This twenty-year-old boy developed diabetic coma at the age of seven. His parents were indigent and emotionally inadequate, and he grew up in an extremely disturbed environment which included several foster homes. Control of glycosuria was poor, and there were repeated hospitalizations for infections. He had many self-induced as well as unintended insulin reactions. At sixteen he omitted insulin while on a food spree and developed diabetic coma. Psychiatric evaluation at that time suggested that the patient's anger and hostility toward his condition often led to resentful deviation from his diet which in turn was followed by self-directed anger. At twenty, after a period of turmoil which appeared to stem from his unsuccessful effort to develop a vocation, he re-entered the hospital for control of his diabetes. It was observed by house officers and nurses that he was withdrawn, suspicious, hopeless about the future and depressed. Several days later he committed suicide by jumping from a fifth-floor window.

This patient's history illustrates several characteristic self-destructive behavior patterns. He had often induced insulin reactions or given up his diet in reaction to difficult life situations. The existence of self-directed anger was first observed at the age of sixteen. The final and decisive act came when the need for making a major adjustment in face of the handicap of diabetes and inadequate personal resources resulted in a feeling of futility and hopelessness.

Case 2, J.G. This hemophilic boy, who had suffered several musculo-skeletal deformities as a result of hemarthroses, was found to have diabetes at the age of twenty-one. He accepted the diagnosis with apparent imperturbability, but that this was in part a denial became obvious when, after the first few months, he abandoned his diet, gained thirty pounds, and refused insulin injections out of fear of bleeding, although needle punctures were known to be safe. At this time he also began to mention somewhat grandiose fantasies about his future vocation. Six months later, when he was hospitalized for hepatitis and treated with a high carbohydrate diet as well as insulin injections, he became depressed and threatened to jump from a window. Following transfer to a state hospital, he improved somewhat, although he slashed his wrists one week end during a home visit. He was finally given a trial discharge, but once home, he refused food and insulin for the expressed purpose of killing himself, and prevented medical consultation by threats of violence. When he was finally hospitalized in deep diabetic coma he did not recover.

Obesity did not develop in this boy until after diabetes had been discovered and the need arose to limit the food intake. Neither depression nor suicidal tendencies had been noted prior to the hepatitis and enforced treatment with diet and insulin. At this time, the patient used his diabetes to commit suicide.

Case 3, T.D. This twenty-two-year-old girl developed diabetes at the age of fourteen following a ten-month period in which her mother and two siblings died of cancer or tuberculosis. Her father sent her to live with a much older sister whom the patient came to consider strict and unloving. The sister, on the other hand, found the patient to be an overly dependent child who demanded that her diet be prepared for her and that all the materials for the insulin injection be readied for her each morning. Whenever the patient felt rejected or unloved, she abandoned her regimen. At the age of eighteen she was asked to live temporarily with relatives while the sister assumed the care of another ill sibling. The patient left home without her insulin and syringe and was hospitalized four days later in diabetic coma. Subsequently the patient married, had a child, and repeatedly suffered severe insulin reactions. Her husband noted that she would frequently refuse to eat after taking insulin and it was suspected that at times she took more than her usual dose of insulin.

Although this patient's behavior may have had multiple motivations, much of it was essentially self-destructive and usu-

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ally occurred when she felt unloved and unwanted.

Case 4, E.L. This twenty-year-old girl developed diabetes at the age of seven but was not a problem in management until the age of twelve when she rebelled against diet, would not test her urine, refused to carry sugar with which to treat her frequent insulin reactions, was poorly controlled, and often avoided visiting the doctor or dietitian. She resented sympathy, became angry when her family mentioned her illness to others, and felt that going to a camp for diabetic children "labeled" her. The mother was both hostile and overanxious, the father was indifferent, and the younger sister informed on her whenever she ate candy or ice cream. The patient's marriage at nineteen was unhappy, and during a marital crisis, after some days of mishandling her diet and insulin in a way that was inconsistent with what she had been taught and knew very well, she was admitted to the hospital in a condition of acidosis.

Subsequently the patient admitted that when she was unhappy and felt unwanted or unloved, she became depressed and "did not care what happened."

DISCUSSION

Many factors in the lives of young diabetic patients make personal adjustment difficult. Control of the diabetes suffers correspondingly so that good control over a period of years is observed in only a minority of juvenile diabetics.[1,2]

Some of the ways in which the physician may fail the patient have been described elsewhere,[3] but discussion of the reasons for failure of juvenile diabetics in treatment have usually not emphasized the self-destructive motivations in their behavior.[4-12]

The same reasons may operate in the adult as well as in the juvenile diabetic, but it is in the latter that self-destructive behavior is more conspicuous. Whereas the adult diabetic has confronted and at least partially resolved the problems of growing up before the onset of his illness, the behavior of the younger diabetic may be greatly influenced by the necessity of working through the adjustments of puberty, adolescence, vocation and marriage under the handicap and constant threat of his illness.

The behavior of the young person with diabetes is determined by his personality structure, by the emotional significance of diabetes to him as an individual and by his environment. His reactions find conscious and unconscious expression through the use of the more meaningful symbols at hand. Diet, insulin, the possibility of hypoglycemia or acidosis, and the provoked reaction of his environment to his illness are always available for the expression of current feelings.

Accordingly, many juvenile diabetics at one time or another reject diet, go on food sprees, falsify or refuse to make urine tests, break syringes so that they cannot take insulin, "forget" appointments, engage in jealous bickering with healthy siblings, exhibit temper tantrums or quarrel with parents, or become seclusive and socially ill-adapted. They may show varied combinations of hostility, rebelliousness, negativistic behavior and provocative attitudes or performances.

Even when such a patient has been carefully instructed and has gained experience through previous mishaps, he may continue from time to time to induce severe reactions by insulin overdosage, undereating or hunger strikes, or induce diabetic acidosis through the omission of insulin or through failure to seek treatment for an intercurrent illness.

Outbreaks of such behavior are more likely to occur at critical periods of adjustment when the patient is frustrated, feels rejected or inferior, and considers the future hopeless. When parents have been unable to handle their own feelings about the sick child and become rejecting or hostile, and the economic level of the home is indigent or marginal—influences which have been shown[4-6] to have a critical effect on the young diabetic—the tendency to fall into self-destructive behavior patterns is more likely to become manifest.

Of course, the behavior of a young diabetic patient during a given crisis may have multiple significance. Thus, the induction of an insulin reaction or of diabetic coma by an intelligent and well-instructed patient may simultaneously or alternately express a need for punishment, a wish to be loved and taken care of, the intent to punish a parent, or an urge to self-destruction.

The last-named motivation for disturbed behavior is commonly unrecognized because the intent is not overt. Also, many parents and some physicians may not be sufficiently knowledgeable to understand the situation nor emotionally capable of accepting the existence of such a disturbing tendency in a young person. However, the self-destructive meaning of a patient's behavior may be suspected when it occurs, as can usually be established, in relation to events which have produced despair, hopelessness, feelings of worthlessness and depression. Interviews with patients who have shown such behavior will only rarely elicit an avowal of suicidal intent. More frequently one obtains only an admission of self-directed anger or some expression such as "I would not care what happened."

Information as to the incidence of overt suicide in juvenile diabetics is meager. In diabetics of all ages, the incidence of suicide was 0.3 per cent in the Naunyn era (1898-1914) and 0.5-0.7 per cent in the Banting and Best era (1922-1951).[13] This may be a low estimate. Three of the five young persons who committed suicide in Massachusetts between 1941 and 1950 as a re-

sult of physical illness were diabetic.[14] Attention has also been called by Mason[15] to the existence of diabetes as the background illness for the suicidal behavior of three disturbed adolescent girls. Moreover, a significant proportion of cases of coma in young persons may actually be attempted suicides; Rosen and Lidz[16] found that ten out of twelve patients who had repeatedly been in coma had actively or passively brought about acidosis in an attempt to escape difficult life situations.

It cannot readily be determined whether self-destructive behavior is peculiar to the young diabetic patient without studying other young persons with other chronic illnesses such as tuberculosis, rheumatic fever and epilepsy. Such patients as well as juvenile diabetics experience their chronic illness as a defect which sets them apart from their own group.

However, the young diabetic suffers much more intensely from limitation of food than other sick young people and this frustration of a basic satisfaction may predispose him to depression.[17] Not only does he lose freedom to gratify hunger without penalty (glycosuria, complications) but food begins to be regarded as a kind of poison which requires an antidote, e.g., insulin.[7] Furthermore, parental limitation of eating may be experienced as a recurrent manifestation of rejection or hostility, which indeed frequently exists. The young person with diabetes often behaves as though hostility and rejection—not the diabetes—were the reasons for the penalties and dangers associated with breaking the diet. Gross dietary infractions and other forms of self-neglect then become conscious or unconscious methods of striking back and punishing a parent who is felt to be unloving.

The use of the so-called "free diet" might help the physician and the parent more easily to avoid strict, overcritical and punitive attitudes with respect to food[18,19] but considerable evidence points to the importance of normoglycemic control as a major factor in reducing the incidence and severity of complications.[1,2,20,21] Unfortunately, even with accepted methods of management, continuous good control and avoidance of severe complications can be brought about only in a minority of young patients with diabetes[1,2] because physiologic difficulties in management are often compounded by emotional problems.

While better results may ultimately be obtained with advances in treatment, it would seem more feasible at present to improve therapeutic results by recognizing, understanding, and treating the emotional difficulties of the juvenile diabetic patient. Problems are usually recognized far too late to be treated effectively. The ostensible reasons which patients advance for bizarre or inadequate behavior should always be examined with great care to determine whether they are realistic explanations or merely rationalizations. It is of great importance to determine how the juvenile diabetic attempts to ward off anxiety with respect to his illness. "Denial" of the diabetes is a common defense. The patient behaves as though he were not a diabetic and as though he were either indifferent to or oblivious of the real dangers of his illness. As with other unrealistic denials, this attitude must not be dealt with precipitously and crushingly before the patient has been helped to acquire other means of support. The attempt to bring the young diabetic to a realistic view of his illness must be gentle and gradual. In those patients who seem incapable of realistic behavior, the physician must be willing to compromise and settle for the level of care the patient is able to accept.

Much environmental manipulation may be needed, particularly if the patient's parents are themselves disturbed persons in their approach to the child and his diabetes. Parents may need to be helped with their own problems before they can become a source of support for the child.

Such an approach to the young diabetic requires the assistance of the social worker and the psychiatrist much more often and much earlier in the course of the diabetes than has usually been the case in the past. All juvenile diabetics should be evaluated psychiatrically at the time the diagnosis of diabetes is first made and periodically thereafter. Usually, neither the physician, the social worker, nor the psychiatrist can improve the management of the juvenile diabetic *after* self-destructive ways of handling his diabetes have become an accustomed way of life.

SUMMARY

Many young diabetic patients exhibit a gamut of unreasonable behavior which can be interpreted as essentially self-destructive. While similar behavior may occur in adult diabetics and in other chronic illness, it is in the young patient with diabetes in whom a conscious or unconscious self-destructive reaction to life problems is most prominent. Various aspects of the treatment of diabetes and the possible complications of the disease afford such patients ready means for self-destructive acting out. Such behavior is most frequently exhibited when major life adjustments must be made, and are more likely to occur when the emotional and socioeconomic environment is suboptimal. It is therefore essential in the treatment of juvenile diabetic patients to

investigate the early manifestations of such behavior and to attempt to avoid more serious difficulties by manipulation of the environment and by a gentle, gradual adjustment of the young diabetic to a more realistic view of his illness and his problems. Since the situation is usually irretrievable when self-destructive ways of handling diabetes have become an accustomed behavior pattern, it would be desirable to interview young diabetics psychiatrically at the onset of the disease and periodically thereafter.

SUMMARIO IN INTERLINGUA

Comportamento Auto-destructive in Juvene Patientes con Diabete Mellite

Multe juvene diabeticos exhibi un extense spectro de habitudes irrational que pote esser interpretate como essentialmente auto-destructive. Il es ver, simile formas de comportamento es incontrate etiam in diabeticos adulte e in patientes con altere morbos, sed il es in le juvene patiente con diabete que conscie o subconscie reactiones auto-destructive verso le problemas del vita es le plus prominente. Varie aspectos del tractamento de diabete e le semper possibile complicationes del morbo provide tal patientes con ample opportunitates pro traducer lor auto-destructivitate in actiones. Tal formas de comportamento es exhibite le plus frequentemente quando major adjustamentos a nove problemas del vita debe esser effectuate, e lor occurrentia debe esser expectate con le plus alte grado de probabilitate quando le ambiente emotional e socio-economic es minus que optimal. Per consequente il es essential in le tractamento de juvene patientes diabetic investigar le precoce manifestationes de tal tendentias e essayar evitar plus serie difficultates per le manipulation del ambiente e per le adjustation dulce e gradual del juvene diabetico a un conception plus realistic de su morbo e su problemas. Viste que le situation es usualmente irreparabile quando le patiente ha establite un attitude auto-destructive verso su diabete como un forma costumari de comportamento, il pare desirabile instituer interviews psychiatric pro juvene diabeticos al initio del morbo e subsequentemente a intervallos periodic.

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Vascular Disease in Juvenile Diabetic Patients of Long Duration

A Preliminary Report

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The introduction of insulin to medical practice was followed by a remarkable improvement in the physical state of diabetic patients. However, it is obvious that with increased expectancy of life, they are prone to a greater incidence of vascular disorders compared to other members of the community. Furthermore, these changes differ from those seen in nondiabetics. It is disturbing, after more than three decades of insulin therapy, to realize that the reason for this is still unknown.

For many years the term "degenerative" has been applied to arteriosclerotic change, implying that blood vessels wear out in much the same way as a piece of hose. It is remarkable that little attention has been paid in recent years to studies of the arterial wall as a living tissue subject to the influence of humoral factors known to affect the metabolism of other bodily tissues.

Most of the attempts to explain the occurrence of premature vascular changes in diabetic patients have been related to clinical management and are concerned with observations on hyperglycemia and glycosuria. It must be obvious that any assessment of the successful management or "control" of patients of long duration can only be related to intermittent observations of the level of blood sugar or glycosuria. It is questionable whether such evidence can ever be sufficiently accurate to support the dogmatic conclusions which have been made.

No simple clinical test has yet been devised to provide an estimate of the daily control of protein or fat metabolism. Yet this information could be of equal importance in any long-term study of vascular disease. The advent of the sulfonylurea drugs and our lack of precise knowledge of their mode of action only serve to emphasize the difficulties of defining control of diabetic patients.

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It cannot be denied that failure to establish normoglycemia could be related to the lack of a perfect therapeutic preparation of insulin capable of exerting a true homeostatic effect on the disturbed metabolism of human patients. If this had been available vascular disease might have ceased to be a problem. However, it must not be forgotten that vascular changes occur in middle-aged diabetics whose diabetes seems capable of adequate control by dietary restriction alone.

In recent years, evidence has been presented which suggests that the vascular changes seen in patients inadequately controlled by conventional standards do not differ significantly from those found in patients considered to have been well controlled.[1,2] This has prompted an investigation into a group of juvenile diabetic patients of long duration in an attempt to determine whether any other factors might be responsible for premature vascular change.

MATERIAL AND METHODS

Forty-seven patients, all of whom developed diabetes mellitus before the age of twenty-one years and who have had diabetes for more than twenty years, have been studied for evidences of vascular change and an attempt has been made to relate its occurrence to control. Each was subjected to a complete physical examination. In addition to routine clinical examination of the cardiovascular system, screening of the heart was undertaken in any instance where doubt existed as to cardiac function. Electrocardiograms were taken from every patient and were considered independently by a cardiologist, Dr. J. M. Gardiner. The state of the peripheral circulation was assessed by examination of the peripheral pulses and by oscillometric readings on the leg vessels in every patient. Retinoscopy was performed on all patients by Mr. James Foster, a senior ophthalmologist. Urinalysis for the presence of albumin and for microscopic abnormalities was undertaken in all patients and renal function tests were performed in all doubtful cases. Biochemical estimations of serum lipids were made

in sixteen patients and electrophoretic studies of serum lipids were performed on the plasma from most patients in the series. The presence or absence of insulin inhibitors in the serum of twenty-two patients was determined by Dr. J. Bornstein.[8] The assistance of our colleagues in providing independent opinions has proved of value in obtaining an unbiased assessment of the present physical state of the patients in this group.

Almost all of these patients have been under the observation of one of us (E.D.) for many years and with few exceptions, records extending for more than twenty and in some instances more than thirty years were available for analysis. Each patient was assessed independently. A careful history was compiled from the patients' own experiences, from the evidence of parents and from a survey of medical records. Particular attention was paid to insulin requirements during the diabetic life, to episodes of ketosis or severe hypoglycemia, and to any other significant events during adolescence or early adult life. The family history of each patient was carefully investigated and the obstetrical history of each married female was recorded.

From the data obtained, an attempt was made to estimate the present state of the vascular system of each patient and to relate it to conventional criteria of control, to the diabetic age, to the daily insulin requirements and to the presence or absence of insulin inhibitory factors in the plasma.

From the commencement of this analysis two difficulties were apparent: The first was concerned with criteria of control and the means of expressing this; the second with criteria of vascular change. The expression of both of these involved clinical impressions and the use of abstractions such as "good," "fair," and "poor" can only be regarded as sincere approximations. Assessment of control of hyperglycemia and glycosuria over a period of twenty or thirty years presented considerable difficulty and the data on each patient were too massive to reduce to simple tabular form. The same difficulty was encountered in classifying the vascular changes. Apart from grouping retinal findings, which can be done with some certainty, attempts to describe the entire vascular state of any individual patient again involved the use of the words "good," "fair" and "poor."

With these reservations, it is desirable to define these terms as applied to the patients under consideration. "Good control" has been applied to patients who, apart from episodes of incidental ketosis due to infection or other circumstances outside the individual's control, were known to be careful and regular in habit, to cooperate closely in treatment and to be regular in attendance for supervision. In addition, records of urinalysis and of blood sugar analysis indicated that over the years these patients had been noted as aglycosuric and normoglycemic. "Fair control" was applied to those who, because of difficulty in maintaining stability of diabetes or through carelessness or temperament, had experienced unnecessary episodes of ketosis, and whose urine tests and blood sugar estimations indicated the existence of glycosuria and hyperglycemia at intervals throughout the years of observation. "Poor control" has been applied to those patients who, apart from continuing a daily dose of insulin, paid scant regard to dietary care or to urine examinations, who have been irregular in their medical supervision and who have frequently been hyperglycemic and glycosuric.

In assessment of vascular change the term "good" has been applied to those patients who have no evidence of cardiac disease, a normal electrocardiogram, normal blood pressure, normal oscillometric readings, no evidence of renal disease and whose optic fundi revealed no abnormality or at most an isolated microaneurysm. The term "fair" has been applied to those whose optic fundi showed minor changes on retinoscopy or a minor degree of hypertension or a slight intermittent albuminuria. More than one such abnormality designated the patient as "poor," as did severe retinopathy, marked hypertension or definite evidence of renal impairment.

RESULTS

The relationship between diabetic control and clinical evidences of vascular change, of retinopathy and of nephropathy in the forty-seven patients investigated is summarized in table 1. The relationship between the duration of diabetes and of the daily insulin dosage to the vascular state of these patients is shown in tables 2 and 3. From the data presented there seems to be no reason to assume that any direct connection exists between vascular disease and control, duration of diabetes or the daily insulin dosage.

The relationship between the presence of detectable insulin inhibitory substances in the plasma and vascular change in a random sample of the patients examined is shown in table 4. Table 5 shows a comparison between the findings of insulin inhibitory substances and the average daily insulin dosage of these patients. It is apparent that insulin inhibition as demonstrated in vitro by estimation of glucose uptake by the isolated rat diaphragm bears no relation to the insulin requirements of these patients.

There is, however, one significant difference between the patients with clinical evidence of vascular damage

TABLE 1

Relation between diabetic control and vascular state, retinopathy and nephropathy

Patients	Control	Cardiovascular assessment		Retinal change				Albuminuria	
		Normal	Abnormal	Nil	*	†	‡	Nil	Present
17	Good	8	9	10	4	2	1	13	4
23	Fair	10	13	14	6	2	1	19	4
7	Poor	2	5	4	0	1	2	3	4

* Isolated microaneurysm.
† Retinal exudate or hemorrhage.
‡ Extensive retinitis, detachment or retinitis proliferans.

TABLE 2

Relation of vascular state to duration of diabetes mellitus

Patients	Diabetes (years)	Vascular state		
		Good	Fair	Poor
13	30	8	5	0
34	20-30	12	17	5

TABLE 3

Relation of vascular state to average daily insulin dose

Patients	Insulin dose per day	Vascular state		
		Good	Fair	Poor
16	>60	9	6	1
23	40-60	9	12	2
8	<40	2	4	2

TABLE 4

Relation of vascular state to presence of insulin inhibitors in plasma

Patients	Inhibitors in plasma	Vascular state		
		Good	Fair	Poor
8	Nil	8	0	0
14	Present	2	7	5

TABLE 5

Relation of insulin inhibitors in plasma to average daily dosage of insulin

Patients	Inhibitors in plasma	Average insulin dose U./day		
		>60	40-60	<40
8	Nil	3	4	1
14	Present	6	5	3

and those who showed minimal or no vascular change. In the former group insulin inhibitory substances were present in the plasma of twelve patients with vascular change and also in two with no clinical evidence thereof. In the remaining eight patients with no evidence of vascular damage insulin inhibitory substances were not demonstrated in the plasma.

Electrophoretic and lipid studies were made on the serum from over thirty patients in the series, all of whom were suitably prepared by abstention from fat before the tests were undertaken. The results of the lipid analyses showed no significant difference between the patients with no evidence of vascular change and those with early evidence thereof. All the patients with obvious vascular damage showed the usual pattern of increase in β lipoprotein, cholesterol, fatty acids and total lipids. No significant difference was found in the electrophoretic patterns of the patients with good vascular state and those classified as fair.

Two incidental observations were made during the course of this study. The first was the finding of an unusually high incidence of a family history of diabetes. Thirty-two of the forty-seven patients gave a history of diabetes in some member of an earlier generation, an incidence of approximately 69 per cent. The second was concerned with the obstetrical histories of the women in this series. In tables 6 and 7 the numbers of stillborn and living children are related to the vascular state and to an assessment of the diabetic control of the mothers. With very few exceptions all these patients were under the care of one obstetrical service throughout their pregnancies.

DISCUSSION

In selecting a group of juvenile patients for investigation it was felt that an assessment of patients in earlier age groups when vascular disease is seldom seen in non-diabetic subjects would disclose evidence of vascular change more clearly than in later periods of life.

A vast literature has been developed to support the doctrine that strict control prevents or delays the onset of vascular change and this view is firmly held in

TABLE 6

Relation of vascular state to outcome of pregnancy

Patients	Vascular state	Pregnancy	
		Living	Stillborn
7	Good	9	5
11	Fair	3	10
1	Poor	1	0

TABLE 7

Relation of control to outcome of pregnancy

Patients	Control	Pregnancy	
		Living	Stillborn
7	Good	5	6
10	Fair	9	8
2	Poor	2	0

many clinics throughout the world. It is only recently that contrary views have been expressed as has been emphasized by Danowski:[4] "Perhaps the most pernicious effect of the view that strict regimentation prevents the vascular complications of juvenile or other long-term diabetes is the distraction of the interest of clinicians and investigators from studies of alternative views." Both Gerritzen[5] and Jackson[6] have postulated that vascular disease and diabetes may stem from a common cause. They suggest that the development of vascular disorders bears no relation to the clinical management of diabetes as practiced today. Larsson, Lichtenstein and Ploman[3] have stated that clinical control had no influence upon the development of vascular changes in a large group of juvenile diabetics under their care for many years. The studies of Aarseth[7] and of Lundbaek[8] are in agreement with this view. Danowski's survey of a group of children with diabetes of ten to twenty years' duration also supports the idea that other factors are concerned. The rare instances of spontaneous improvement or disappearance of vascular lesions, and the benefit which sometimes follows hypophysectomy, emphasize the need for a fresh approach to the problem.

The material presented in this study provides no support for the view that control has any influence on the presence or absence of vascular lesions. It is quite striking that several patients who have had diabetes for over thirty years with no signs whatever of vascular change must be classified as among the worst-behaved when judged by conventional standards. No significant relationship has been found between the duration of diabetes, the range of insulin dosage or the electrophoretic pattern of the plasma and the occurrence of vascular disease. While the greatest incidence of change has been observed in the retinal patterns of these patients this may merely reflect the fact that this is the one area of the body which readily presents blood vessels for direct inspection.

It is neither possible nor desirable to make dogmatic statements on a limited experience with a small number of patients. The number of cases classified as poorly controlled seems remarkably small. It could be that some, who treated their complaint with contempt, are now dead because of their own neglect or from lack of adequate supervision during the war years. The failure to establish a clear relationship to control and the difference which apparently exists in the presence of insulin inhibitory substances in our patients may be of significance. Observations are proceeding in a similar age group on patients who have arterial disease of nondiabetic origin. In addition a group of elderly diabetic and nondiabetic patients is being investigated in an attempt to determine the importance of this finding.

While the benefits of insulin therapy are universally recognized, its use in clinical practice cannot be regarded as similar to the exhibition of thyroid extract in cases of thyroid deficiency. If diabetes mellitus and its vascular complications are solely concerned with insulin deficiency, both should be capable of correction indefinitely by substitution therapy. It seems that there must be other unknown factors which are responsible for the vascular change.

A possible relationship between insulin inhibitory substances and vascular disease has been observed. While the importance of this observation is not clear, it has prompted further studies to determine whether these substances are related to the development of vascular changes or whether they are merely a consequence of an etiologic factor as yet unknown.

SUMMARY

Forty-seven diabetic patients, all of whom developed diabetes before the age of twenty years and who had histories of more than twenty years, have been examined in an attempt to ascertain the relationship between control of diabetes and the development of vascular sequelae.

No relationship has been established between the presence of vascular damage and the adequacy of control, the insulin dosage, or the duration of diabetes.

A relationship seems to exist between the occurrence of vascular disease and the presence of insulin inhibitory substances in the serum of these patients.

The significance of this finding is unknown. Studies are proceeding and the hope is expressed that they may

provide a new approach to the problem of diabetic vascular disease.

SUMMARIO IN INTERLINGUA

Morbo Vascular in Patientes con Diabete Juvenil de Longe Duration—Un Reporto Preliminari

Quaranta-septe patientes diabetic—omnes con diabete depost ante lor vintesime anno e omnes vivente con ille condition depost plus que vinti annos—esseva examinate con le objectivo de determinar le relation inter le "stabilisation" de diabete e le disveloppamento de sequellas vascular.

Nulle correlation esseva constatate inter le presentia de insultos vascular e le adequatia del "stabilisation," le dosage de insulina, o le duration del diabete.

Un correlation pare exister inter le occurrentia de morbo vascular e le presentia de substantias insulino-inhibitori in le sero.

Le signification de iste facto non es cognoscite. Studios concernite con iste problema es in progresso. Le spero es exprimite que iste studios va aperir nove avenues de attacco relative al problema de morbo vascular in diabete.

ACKNOWLEDGMENT

Our thanks are extended to Mr. James Bryan Foster, F.R.C.S., for his assistance in examining the eyes of all patients in this series. We also thank Dr. James Gardiner for his opinion on the electrocardiograms and for his assessment of the cardiac state of our patients. The estimations of blood lipids were made by Miss June Sheath, M.Sc., whose assistance is gratefully acknowledged.

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When the ultraviolet absorption characteristics of pure methylarachidonate were compared with those of the isomerized C_{20} polyunsaturated fatty acid fractions from linoleate-fed and linolenate-fed animals, it was evident that there was an excess of from 3.5 to 6.0 per cent pentaene or hexaene acids in the fat from the linolenate-fed animals. These observations conform with the results of R. Reiser (*J. Nutrition* 42:325, 1950). Some presumptive evidence from columns in which incomplete separation of a portion of the C_{20} unsaturated fatty acids was obtained, indicated that most of the radioactivity in this fraction was present in the C_{20} pentaene acids. There was very little activity in the linoleate isolated directly from the main bromination mixture.

In summing up their observations, the authors state that if linolenate is converted to arachidonate it is not reduced to linoleate as the first step. Thus, if the Δ^{15} double bond is reduced, it evidently is not reduced until after the chain lengthening step has occurred. In view of the evidence from this study and that of others regarding the conversion of linolenate to more highly unsaturated fatty acids (Reiser, *loc cit.*; Houton et al., *J. Am. Chem. Soc.* 76:4970, 1954) it seems likely that linolenate "is converted to C_{20} and C_{22} pentaene and hexaene acids, possibly via a C_{20} tetraenoic acid isomeric with arachidonic acid." Thus the difference in the biological activity of linoleate and linolenate (Hume et al., *Biochem. J.* 34:879, 1940; Greenberg et al., *J. Nutrition* 41:473, 1950; Thomasson, International Conference on Biochemical Problems of Lipids, Brussels, p. 212, 1953) would appear to have a metabolic basis.

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Electrophoretic Distribution of Allergenic and Hormonal Fractions of Commercial Insulins

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Allergic reactions following insulin administration have frequently been considered to be due to the insulin molecule itself, rather than to impurities in the commercial product. This latter possibility was originally suggested by Banting in 1922, but, as commercial preparations became more refined, such impurities were considered less significant. Upon availability of crystalline insulin, many investigators assumed the preparation to be devoid of impurities, and that the responsible allergen, when demonstrated, was insulin itself. Renewed interest in further purification of crystalline insulin was stimulated by Jorpes[1,2] who studied the effects of recrystallized insulins in appropriately allergic patients. He concluded that the allergic manifestations caused by the commercial product were due to impurities, rather than to the insulin molecule. Although this appeared to demonstrate the nonallergenicity of sufficiently recrystallized insulin, the allergens concerned have, as yet, remained unisolated and unidentified. In two patients at the Veterans Administration Hospital, Long Beach, California, who displayed both local and generalized allergic reactions to several commercial forms of insulin, the hormone and the associated allergens of these preparations were separated by paper electrophoresis and identified by skin tests and by rabbit assays for insulin activity.

CASE REPORTS

Case 1. L.S.: A thirty-year-old male aircraft worker was found to have asymptomatic glycosuria in November 1953. In February 1954, he entered this hospital with manifestations of uncontrolled diabetes mellitus. There was no personal or family history of allergic disorders. Physical examination disclosed no significant abnormalities. Blood sugar (Folin-Wu) was 420 mg. per 100 ml. A urine specimen tested 3-plus for sugar, negative for acetone. He was put on a strict diabetes regimen, including divided doses of regular insulin (Iletin) initially. After a few days, he was changed to NPH insulin, achieved acceptable control on 60 U. daily in a single morning dose and was discharged from the hospital. Control was maintained without incident until July 1, 1954, when, a few hours after his usual insulin injection, he noted loud borborygmi, became nauseated, and vomited. Each day thereafter, from one to four hours after insulin, a similar episode recurred, without apparent loss of control of diabetes. One week after onset, the patient discontinued the insulin, but continued to vomit a few times each day. Polyuria, thirst, and rapid weight loss ensued, and he re-entered the hospital July 20, 1954, exhibiting moderate dehydration, 4-plus glycosuria, 2-plus ketonuria, and 352 mg. glucose per 100 ml. blood, without ketoacidemia. One hour after subcutaneous injection of 20 U. of regular insulin (Iletin), massive hives appeared over the upper back and all extremities, accompanied by induration, redness, and itching at the site of injection. Oral Benadryl administration appeared ineffective, but hives were absent on the following day when he was intradermally tested (table 1). Iletin Lente, 1 U., gave the least skin reaction. One-half hour later 20 U. of this preparation were injected subcutaneously. Except for a 4 by 5 cm. area of induration with redness and local itching, there were no untoward effects. Vomiting ceased. Dosage was increased to 40 U. daily. Within a week, local reactions decreased in severity and disappeared, and good control of the diabetes was obtained. He continued to show positive skin tests to various insulin preparations and certain of their fractions obtained by paper electrophoresis, as summarized in table 1. After two months without any symptoms, mild itching of the trunk and extremities occurring one hour after injection of Iletin Lente daily and persisting several hours was noted. Antihistamines were of no benefit. No other symptoms have appeared, and the diabetes continued in excellent control on 35 U. daily of Iletin Lente.

Case 2. C.R.: A thirty-three-year-old truck driver developed symptomatic diabetes mellitus in 1947, for which he received a diet and daily injection of a mixture of regular and Protamine Zinc insulins, 45 U. each. There were no allergic reactions of any kind known prior to or with this regimen, and none occurred over the next six and one-half years despite three further hospitalizations for episodes of severe ketosis without coma. On no occasion did he receive other than regular or PZI preparations in this period. In July 1954, he again entered the hospital because of severe fungus infection of the feet and hands. At this time he was transferred to NPH insulin (Iletin NPH), 80 U. daily. Within twelve hours of the first injection, substernal discomfort, wheezing respirations, dyspnea, conjunctival injection, and generalized pruritic urticaria appeared. Intradermal

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tests revealed no reaction to either regular (Iletin) or Lente (Iletin Lente) insulins. With the patient regulated on the latter insulin, 80 U. in one daily dose, all allergic manifestations promptly subsided. Another physician inadvertently changed the insulin prescription to a mixture of regular and Protamine Zinc insulins, 45 U. each. In the following two weeks the patient exhibited an eczematoid rash in the flexural regions and frequent paroxysms of expiratory wheezing terminated by expectoration of viscid colorless material. These manifestations subsided completely within a week of return to Lente insulin as before. The results of intradermal tests are summarized in table 1 (Case 2).

TABLE 1

		Patient in Case 1	Patient in Case 2
Regular insulin (Iletin U-80)			
	1:1	3 2 4 4 1	0 2
	1:10	2 3	0 2 2
Electrophoretic fractions			
Fastest 28-34 cm.		0 0 0 0 1 1 1	0 0 1 0
Main 23-28 cm.		2 0 0 2 2 2 2	0 0 0 0
Tailing 1 16-23 cm.		4 3 4 1 3 3 4	0 0 0 0
Tailing 2 10-16 cm.		4 4 3 2 4 4 4	0 0 0 0
Slowest 0-10 cm.		4 3 3 0 4 3 4	0 0 0 0
Lente Insulin U-80 (Lilly)			
	1:10	2 1 3 4 1	0 0 0 0
Electrophoretic fractions			
Fastest 28-34 cm.		0 0 0 0 0 0 0	0 0 0 0
Main 23-28 cm.		0 0 0 1 0 0 0	0 0 0 0
Tailing 1 16-23 cm.		0 0 0 2 0 1 0	0 0 0 0
Tailing 2 10-16 cm.		0 0 0 0 0 2 1	0 0 0 0
Slowest 0-10 cm.		0 0 0 0 0 2 1	0 0 0 0
Boiled Lente	1:10	2	
NPH Insulin U-80 (Lilly)			
	1:10	2 2 3 4	2 3 3
Electrophoretic fractions			
Fastest 26-33 cm.		2 1 2 0	2 0 2 1
Main 20-26 cm.		0 1 0 0	0 0 0 0
Tailing 1 14-20 cm.		2 1 0 2	0 0 0 0
Tailing 2 1-14 cm.		0 2 0 2	0 0 0 0
Slowest minus 9 to 1 cm.		0 0 0 0	0 0 0 0
Globin Insulin U-80			
(Burroughs Wellcome)	1:10	2 4 4 4	3 1 3
Fraction 1 minus 4 to 3 cm.		0 2 2	2 2 3
2 3-12 cm.		2 2 3	0 2 2
3 12-22 cm.		2 2 3	0 1 2
Protamine Zinc Insulin (Lilly)			
	1:100	2 2 3 3	3 3 3
Beef protein		0	0
Lamb protein		0	0
Pork protein		0	0
5X recrystallized insulin (Lilly Lot T-2842) U-50 1:1		0 0	
Trypsin-treated zinc-insulin crystalline low glucagon-beef source U-50 (Lilly Lot 466368)		4 4	
Trypsin-treated zinc-insulin crystalline low glucagon-pork source U-50 (Lilly Lot 499667)		4 4	
Regular zinc-insulin crystalline beef source U-50 (Lilly Lot 535664)		4 4	

MATERIALS AND METHODS

Fractionation of insulin preparations: In an effort to isolate and identify the allergens in the various insulin preparations, the following were subjected to paper electrophoretic separation:

1. Iletin U-80 (Regular Insulin, Lilly)
2. Lente Insulin U-80 (Lilly)
3. NPH Insulin U-80 (Lilly)
4. Globin Insulin U-80 (Burroughs Wellcome)
5. Five-times recrystallized insulin (Lilly, Lot T-2842)

Each preparation was lyophylized and its residue redissolved in 1.0 cc. of barbital buffer (pH 8.8; μ 0.1), except for Lente insulin and Globin insulin, which did not completely redissolve. Each solution was transferred to five strip "sandwiches" of Whatman 3 mm. paper and subjected to electrophoresis by the technic of Kunkel and Slater[3] at room temperature with a potential of 300 volts for twenty hours. The middle strip was stained with bromphenol blue to determine the protein distribution. Globin insulin did not move from the starting spot under the conditions employed. All other preparations moved toward the cathode, each showing a fast-moving component with variable amounts of "trailings." Since the main component was the only one demonstrable for the five-times recrystallized insulin, it was assumed to be insulin, free of contaminants. Protein concentration along the stained electrophoretic strips was determined by cutting the paper into 2 cm. segments perpendicular to the direction of migration, eluting the bromphenol blue with 2 per cent Na_2CO_3 in 50 per cent aqueous methanol, and determining the dye concentration in a Klett-Summerson spectrophotometer with a 540 mμ filter. Curves representing the protein concentrations in the various fraction were obtained by plotting the densities against the distance from the origin. The protein pattern was arbitrarily divided into five portions, representing the slowest and middle fractions of the tailings, and the slowest, middle, and fastest fractions of the main peak (figure 1). The protein was then eluted from the corresponding sections of the four unstained electrophoretic strips by saline, freed of barbital buffer by extensive dialysis against water and saline, and concentrated to a small volume by lyophilizing. These fractions were then used for skin testing, insulin assays, and precipitin tests.

Skin tests were performed by injecting 0.1 cc. of the test solution intradermally in the volar forearm area. They were observed continuously during development and read at an interval of twenty minutes after injection. Criteria for quantitation of skin reactions were as follows: test wheal equal to or less than area of control wheal (saline in the case of the commercial preparations and diluted barbital buffer in the case of the

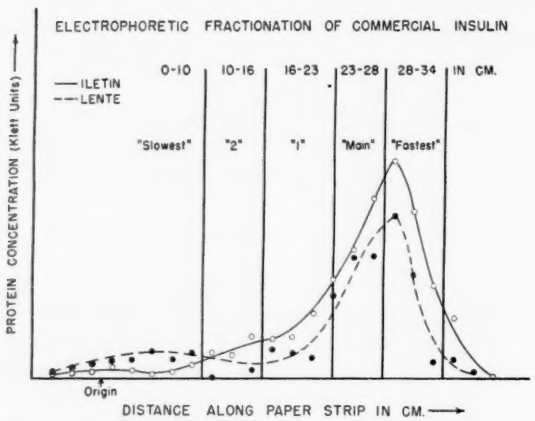

FIGURE 1

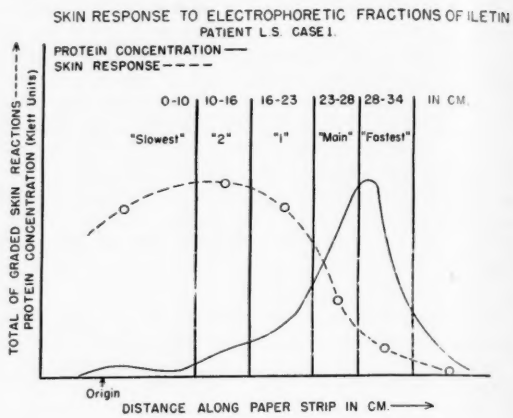

FIGURE 2

fraction obtained by electrophoresis); 1 plus—test wheal greater in area than the control wheal, but without surrounding erythema, pruritus, or pseudopods; 2 plus—test wheal displayed surrounding erythema, but no pruritus or pseudopods; 3 or 4 plus, depending on degree—test wheal displayed erythema, pruritus, pseudopods, and in some instances, exudation of serum.

Both patients were tested at intervals with undiluted and diluted commercial insulin preparations, and with the fractions of these preparations obtained by electrophoretic separation.

RESULTS

Case 1, L.S. had skin tests consistently positive to all commercial insulin preparations and somewhat less consistently to some of the electrophoretic fractions (table 1). In the skin tests with fractions of regular insulin (Iletin) and of Lente insulin, the allergens appeared to be located in the slower fractions, away from the main peak shown by rabbit assay to be insulin. The graded skin reactions to each of the several electrophoretic fractions obtained from the insulin preparations on successive testings were arbitrarily totaled, and the sums were then graphically related to the electrophoretic pattern (figure 2). This suggested that an inverse quantitative relationship existed between the degree of skin sensitivity and the amount of insulin in each fraction. The electrophoretic pattern of NPH insulin was similar in shape to that of regular and Lente insulin. Globin insulin gave a curve showing a small broad hump which migrated, and a tall sharp peak which did not move from the starting spot. Due to this insufficient migration of the components during electrophoresis, inadequate separation resulted, and the patient showed positive skin reactions to all three fractions of Globin insulin.

Case 2, C.R., had no skin reactions to the undiluted regular and Lente insulins and their fractions, but showed positive reactions to NPH, Globin, and Protamine Zinc insulins and some of their fractions. It is interesting that this patient showed slightly positive skin reactions to the fractions of regular and NPH insulins at the opposite end of the distribution curve from those to which the patient in Case 1 reacted, although neither patient had positive skin reactions to the fraction containing the bulk of the insulin (table 1).

The identity of the insulin fractions was established by crude rabbit assays. The middle fraction of the tailings, assayed in three rabbits with lyophilized eluate at the 10 mg./kg. level, caused an insignificant rise of 3 ± 12 per cent of the blood glucose level after one hour. The middle fraction of the main peak caused a drop of 48 ± 19 per cent after one hour when assayed at the 2 mg./kg. level.

DISCUSSION

Generalized allergic reactions are relatively uncommon, so that the reported incidences in most series probably do not accurately represent the true incidence. Ljung[4] was able to find only seventy cases reported in the literature until 1951.

The generalized reaction may be manifested by generalized urticaria, angioneurotic edema, purpura, vomiting, diarrhea, dyspnea, stridor, arthralgia, sudden circulatory failure, or an eczematoid dermatitis.[6] No immediate deaths due to insulin allergy have been reported to date.

Although Brunn[5] has reported allergic reactions to insulin recrystallized twelve times, Jorpes has found insulin recrystallized three to four times to be sufficiently free of allergens.

A lesser allergenicity of Lente insulin has been described,[2] and this was confirmed in the two cases reported here. Lente insulin was found to be insignificantly allergenic in Case 1 and completely nonallergenic in Case 2. In both instances the patients showed no evidence of allergy to insulin itself, but rather to the allergens found in the noninsulin electrophoretic fractions. The allergens were presumably not species specific, as shown indirectly by negative skin tests to species protein. Their nature remains unknown.

SUMMARY

1. Commercial insulins were subjected to paper electrophoresis and found to be heterogeneous.

2. The insulin fractions were identified by bioassay. All electrophoretic fractions were used for skin tests in two patients who gave clinical evidence of generalized "insulin allergy."

3. Maximum skin reactivity was elicited by the noninsulin fractions in one patient. The second patient had no skin reactivity to regular and to Lente insulin and their fractions, but did show reactivity to NPH, Globin, and Protamine Zinc insulin and some of their fractions.

4. In the two patients studied, "insulin allergy" appeared to be due to materials other than insulin and species specific protein. Their nature remains unknown.

SUMMARIO IN INTERLINGUA

Le Distribution Electrophoretic de Fractiones Allergenic e Hormonal de Insulinas Commercial

1. Insulinas de origine commercial esseva studiate per electrophorese a papiro. Esseva constatate que illos esseva heterogenee.

2. Le fractiones de insulina esseva identificate per bioessayage. Omne le fractiones electrophoretic esseva usate in tests cutanee in duo patientes con indicationes clinic de un generalisate "allergia a insulina."

3. Grados maximal de reactivitate cutanee esseva evocate in un del patientes per le fractiones non-insulinic. Le secunde patiente exhibiva nulle reactivitate cutanee a insulina standard e insulina Lente e lor fractiones, sed reactivitate positive esseva constatate in iste caso pro Insulina NPH-50, Globina, e Insulina a Protamina e Zinc e certes de lor fractiones.

4. In le duo patientes studiate, le "allergia a insulina" esseva causate apparentemente per materiales altere que insulina o proteina a specificitate de specie. Le natura del materiales responsabile pro le reaction allergic remane incognite.

ACKNOWLEDGMENT

We are grateful to Dr. W. R. Kirtley, Clinical Research Division, The Lilly Research Laboratories, for the recrystallized and low glucagon insulins used in this study, and to Miss Lucille Butler, R.N., for the performance of the skin tests.

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The condition of diabetes mellitus caused by pancreatic insufficiency is considered by the authors to reflect a state of a lowered energy potential of the cells and in consequence a lowered capacity to carry out synthetic reactions.

The organs most severely affected are those chiefly concerned with synthetic reactions, the liver and the adipose tissue. Muscle metabolism appears to be affected only in the most severe diabetic state.

Though the diabetic condition manifests itself primarily and most evidently in symptoms indicating a disturbance of glucose metabolism, such as high blood sugar and high rate of urinary glucose excretion, the metabolic reactions affected in diabetes are not only concerned with carbohydrate metabolism, indicating a metabolic disorder affecting a wider range of synthetic reactions such as reduced fat synthesis from small molecules, e.g., pyruvate and acetate, and to some extent also the reduced incorporation of amino acids into proteins.

Thus diabetes is a general metabolic disorder affecting carbohydrate, fat and protein metabolism and this is what makes it so complex a subject for study. According to the ideas of the authors the main metabolic defects in the liver, i.e., the inability to utilize glucose for glycogen and fat synthesis are not specifically due to a defect of glucose metabolism, but to a defect in a superimposed metabolic reaction controlling simultaneously both glucose and fat metabolism.

E. B. Chain, A. Beloff-Chain, and F. Pocchiari, from "Present Knowledge of the Mechanism of the Mode of Action of Insulin," in *Selected Scientific Papers from the Istituto Superiore di Sanità*, Vol. 1, part 3, p. 516, 1956.

Metastasizing Carcinoid with Diabetes Mellitus

Harry Keen, M.B., M.R.C.P., London

Metastasizing carcinoid is rare, but diabetes mellitus is common, affecting by present reckoning about one per hundred of the population.[1] In the absence of a special relationship between the two conditions, one would expect about one in a hundred cases of carcinoidosis also to be diabetic. About 200 well documented cases of the carcinoid syndrome have now been published, only one of them[2] with co-existing diabetes. There can thus be no a priori claim that the case reported here consists of any more than a coincidence of conditions.

CASE REPORT

Mr. J.C., in 1958, was a fifty-one-year-old man working in a sedentary job. In early 1954, he began to experience daily bouts of pain in the left upper abdominal quadrant unrelated to meals or bowel action and unrelieved by alkali. At this time, his bowel habit changed; instead of his normal one formed stool a day, he began to pass up to three, many of which were of loose consistency. After four months of these symptoms, Mr. E. A. Crook, F.R.C.S., of Charing Cross Hospital, performed a laparotomy and found a large primary tumor of the cecum with lymphatic extension and many metastatic deposits throughout the peritoneum. The surface of the liver, particularly its right lobe, was studded with hard nodules. A piece of growth was cut out for examination and the cecal mass was bypassed by anastomosis. Histological examination of the excised tissue showed appearances typical of carcinoid, confirmed by the diazo staining technic[3] (see figures 1 and 2). The patient left the hospital relieved of his pain, which has not recurred.

Towards the end of 1955, he noticed numbness of the right little finger which spread up the ulnar border of the hand. Routine urine examination showed large quantities of reducing substance but no ketone bodies. Fasting blood sugar was 197 mg./100 ml. with the following values at forty-five-minute intervals after 50 gm. glucose by mouth: 360, 340 and 244 mg./100 ml. There was no thirst, polyuria or weakness, nor was there a family history of diabetes. In March 1956 the diabetes was brought under control with 24 U. of Lente insulin daily, with carbohydrate intake restricted to 120 gm. At this time the patient came under the care of the Diabetic Clinic at King's College Hospital. The dose of insulin was gradually reduced and in 1957 completely stopped with no loss of control. Only a slow but progressive loss of weight, and continuing looseness of the stools disturbed the patient.

His slightly telangiectatic complexion was then noted. He had never experienced periodic sensations of heat in the face, and both he and independent observers denied flushing attacks. On examination, there were islands of small dilated vessels chiefly about the nose and chin and slight general ruddiness of the face. In the abdomen the liver was felt on inspiration only; no abnormal masses could be palpated and rectal examination was normal. Loud and frequent borborygmi could readily be heard and had been noticed by the patient. The heart rate was seventy-four per minute and regular; the sounds were normal and there were no murmurs. Blood pressure was 135/80, peripheral pulses were all present, and no abnormality could be found in the nervous or respiratory systems. The optic fundi were normal, but the conjunctival vessels showed definite congestion.

Twenty-four-hour urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA), normally 2-8 mg., was grossly elevated at 188 mg. Paper chromatography of the urine revealed a typical carcinoid pattern with a large 5-HIAA spot, and a smaller one of 5-HIAA ester (Dr. M. Sandler). Hemoglobin was 14.8 gm./100 ml. blood, plasma proteins totaled 6.9 gm./100 ml. with a normal electrophoretic pattern; there was no defect of fat absorption; serum amylase was 280 Somogyi units.

At present the patient is still well enough to do a full day's work though it begins to tire him excessively. In two years, he has lost fourteen pounds in weight at an accelerating rate. The urine is usually sugar-free but occasionally contains up to 0.5 per cent of glucose. Excretion of 5-HIAA is persistently much raised as estimated semiquantitatively by the nitroso-naphthol method.[4]

DISCUSSION

Carcinoid tumors are believed to arise from the argentaffin or Kulchitzky cells of the intestinal mucosa.[5] It was the morphological resemblance of these cells to the alpha cells of the islets of Langerhans and their common affinity for silver which, until 1953, gave rise to considerable speculation regarding glucagon secretion by carcinoid tumors.[6] For this reason, Weisberg and Schaefer[7] looked for evidence of hyperglycemia in 690 published cases of carcinoid, though being unaware of the carcinoid syndrome[8] they did not distinguish between localized and disseminated tumors in their analysis. In only sixty-six cases had blood sugar levels been recorded, of which three showed hyperglycemia. In one of these, a mild diabetic of eight years' duration, the diabetes worsened following removal of a duodenal carcinoid neoplasm.

The patient reported by Fein and Knudtson,[2] a man of twenty-seven years with an eighteen-month history of flushes, diarrhea and colicky abdominal pain, was found to have slight and inconstant glycosuria and a 'diabetic type' of glucose tolerance curve. Laparotomy revealed a carcinoid tumor in the stomach wall

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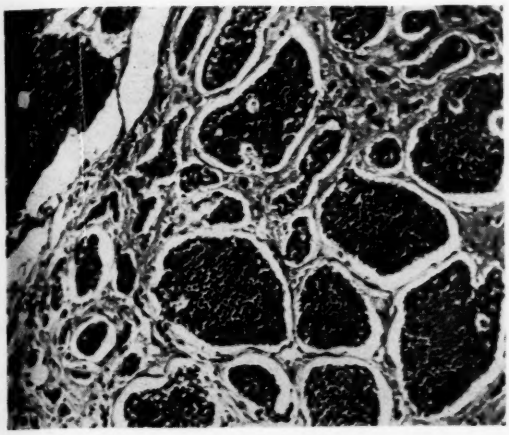

FIG. 1. Typical area of intestinal tumor showing solid cellular masses with fibrous stroma. Hematoxylin and eosin X 104.

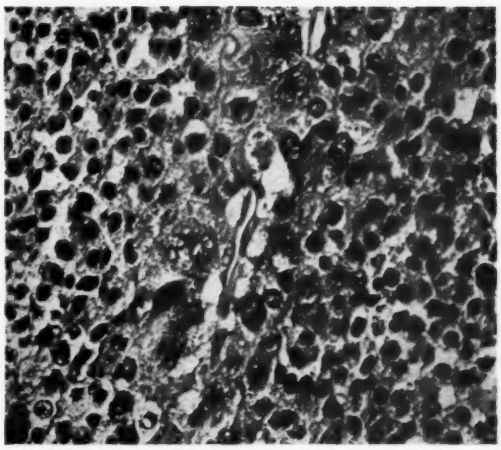

FIG. 2. Area of tumor showing numerous intracytoplasmic granules which are stained an orange red color. Diazo reaction X 400.

and widespread hepatic and visceral metastases, though pancreatic involvement was not mentioned. Increased serum levels of 5-hydroxytryptamine (5-HT, serotonin, enteramine) were demonstrated by bio-assay, and twenty-four-hour urinary excretion of 5-HIAA was 84 mg. The patient's plasma, after treatment to destroy insulin activity, had no greater glycogenolytic activity when incubated with rabbit liver slices than that from a normal control.

Korp and LeCompte[9] reviewed the evidence bearing upon the identity of pancreatic alpha cells and intestinal 'silver cells' and showed that only superficial resemblances existed between them. Many histochemical and vital staining reactions, positive for enterochromaffin cells, were negative for alpha cells; in addition, they demonstrated that cobaltous chloride and Synthalin A produced degenerative changes in the alpha cells but spared intestinal chromaffin cells, confirming similar findings by Hartroft, Wrenshall and Wilson.[10]

It is now quite clear that the main features of the carcinoid syndrome depend upon manufacture by and release from tumor cells of 5-HT;[7] the urinary excretion of large quantities of its principal metabolite, 5-HIAA, is a characteristic pathochemical finding.[11] There have been no reports of the effects of 5-HT upon the blood sugar in man, and the accompanying graph (figure 3) shows the capillary blood sugar response of four normal volunteers to a single intravenous injection of 1 mg. serotonin creatinine sulfate, corresponding to approximately 435 μg. of 5-HT.

J.B., J.R., and H.K. had fasted overnight and T.A. had taken a large meal about ninety minutes before injection. The dose was adequate to produce marked systemic effects, including chest tightness, dyspnea and tingling of the skin, but there was no rise in blood sugar. The two small falls in glucose concentration may have been due to increased glucose extraction during a period of capillary stasis soon after injection.

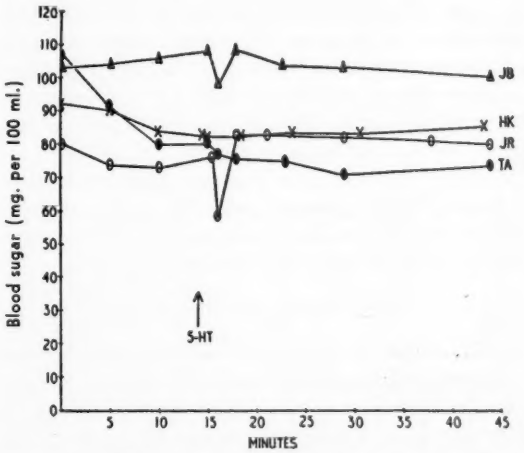

FIG. 3. Capillary blood sugar response to I.V. 5-HT (435 μg.) in four healthy adults. (J.B., J.R. and H.K. fasting; T.A. postprandial.)

The possibility of involvement of the pancreas in the local proliferation of carcinoid tissue found at operation in the present case should be considered. The mild and nonprogressive nature of the diabetes makes it unlikely that pancreatic destruction alone is respon-

sible, a view supported by the absence of evidence of exocrine deficiency and of a palpable abdominal mass. However, the raised serum amylase level may indicate a lesser degree of pancreatic damage, in which case a hyperglycemic response to 5-HT might become manifest; for Sirek[12] has shown that 5-HT produces a blood sugar rise in dogs after, but not before, pancreatectomy.

An unusual feature in this case was the absence of spontaneous flushes despite the considerable quantities of 5-HIAA excreted, similar to the case mentioned by Page[13] and others. It will be of importance to watch for evidence of developing heart disease, for it has been alleged[14] that it may be the violent fluctuations in pressure in the lesser circulation, associated with the flushes, which are responsible for the endocardial damage.

The numbness of the ulnar border of the hand disappeared completely soon after the treatment of the diabetes was started. No supplementary vitamin therapy was given, so it is likely that this was a manifestation of diabetic neuropathy. With two metabolic abnormalities, each alleged to be a potential cause of neurological disorder,[15,16] no disturbance of the central or peripheral nervous system can be found at present.

CONCLUSION AND SUMMARY

A previously recorded case of coexistent carcinoidosis and diabetes mellitus is reviewed and a new case described in a patient in whom secreting carcinoid tissue has been present for at least three years, and diabetes probably for only two. Possible causal relationships between the two conditions are discussed, but chance association is considered to be the most likely explanation.

One milligram serotonin creatinine sulfate given intravenously failed to raise the blood sugar of four normal subjects under suitable test conditions.

SUMMARIO IN INTERLINGUA

Coexistentia de Metastases Carcinoide e Diabete Mellite

Es presentate un revista de un previemente publicate caso de coexistente carcinoidosis e diabete mellite. Es describite un nove caso in un patiente in qui secernente histos carcinoide esseva presente depost al minus tres annos e diabete probabilemente depost solmente duo. Le possibile relationes causal inter le duo conditiones es discutite, sed association accidental es considerate como le explication le plus probabile.

Le administration intravenose de un milligramma de serotonina in complexo con sulfato de creatinina non augmentava le concentration de sucro de sanguine in tests effectuate sub conditiones appropriate in quatro subjectos normal.

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I appreciate the permission to publish this case given by Mr. E. A. Crook and Dr. W. G. Oakley; I would also like to thank Dr. M. Sandler and the Pathology Departments of Charing Cross Hospital and St. Mary's Hospital.

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EDITORIAL

PERINATAL INFANT MORTALITY IN THE UNSUSPECTED DIABETIC

The problem of most concern to the obstetrician today is how to improve fetal salvage. During the past decade we have all witnessed a marked reduction in fetal loss, especially in obstetrical and medical complications of pregnancy. This has been most gratifying in the case of pregnancy in the diabetic woman. The improvement in fetal salvage, which first became evident with the introduction of insulin, has steadily progressed so that viable fetal loss today in many centers is approximately 10 per cent.[1,2] This has been accomplished by cooperative efforts of the internist, obstetrician and pediatrician working as a team. The decreased perinatal mortality has resulted from the almost universal agreement of the need for more adequate prenatal supervision, premature termination of pregnancy and treatment of the newborn as a premature, regardless of its weight or gestational age. Although the choice of the best method to effect delivery and the possible need for substitutional hormonal therapy still remain controversial, further improvement in fetal salvage may be anticipated. This can be accomplished by further education of the laity and physician. Meticulous prenatal care with poor patient cooperation, or excellent cooperation with poor medical supervision are incompatible and result in an increased, rather than a decreased fetal wastage.

Analysis[3-6] reveals that the increased fetal loss in diabetic women starts prior to clinical recognition of the metabolic disturbance and that many of these deaths are preventable. This has been documented by many retrospective studies[3,6,7] that have shown the fetal loss in such cases to be as great as those in the overt diabetic.

This concept is enhanced by the fact that infants born to these mothers have the same embryopathy as occurs in the offspring of the frank diabetic.[8,9] Furthermore, in many instances the pathological changes in the organs of the newborn make the diagnosis of diabetes possible before it is clinically recognized.

This increased fetal loss is preventable in most instances. Prospective rather than retrospective diagnosis and the treatment of these patients as diabetics result in a marked improvement in fetal outcome.[4,10]

Suspicion that an abnormal carbohydrate state exists can be inferred from the past obstetrical history, or the course of the current pregnancy. A family history of diabetes enhances this suspicion. Unexplained intrauterine deaths, recurrent episodes of pre-eclampsia, overweight infants (4,000 gm. or more), or a baby large for the period of gestation, habitual abortions and glycosuria should lead to an investigation of carbohydrate metabolism. This should be made regardless of the fact that the majority of patients so investigated will prove to have no disturbance in carbohydrate metabolism. The value lies in finding those who have hidden diabetes, the so-called prediabetic, so that they can be adequately treated during pregnancy to insure an increased fetal salvage.

For diagnosis of diabetes, reliance should not be based upon the fasting blood sugar and urine tests, for they may be within the normal range as in many known diabetics. Postprandial blood sugars are more informative and therefore preferable. A one-hour-after-breakfast blood sugar (Folin-Wu) between 150 and 170 mg. per cent should be considered as suspicious, whereas a value of 170 mg. per cent or over is definitely indicative of frank diabetes. For those who employ the true sugar (Somogyi-Nelson) on venous blood, approximately 10 mg. per cent less is comparable to the values given above.

However, the best laboratory tool is the glucose tolerance test. It is the most sensitive barometer of carbohydrate metabolism and should be employed in all cases, unless the diagnosis is apparent on the postprandial blood specimen.

Unfortunately there is no one standard method at present for interpretation of glucose tolerance tests. At best, the patient will fall into one of three categories: either frank diabetes, suspicious or probable diabetes, or no diabetes.

If the true sugar method is used, a value of 160 mg. per cent or more in the first hour, 140 mg. per cent or higher in the second hour, and 120 mg. per cent or more in the third hour is considered indicative of diabetes. Normal carbohydrate tolerance would be concluded if the curve falls below 160 mg. per cent for the first hour and below 110 mg. per cent at three hours. Interpretation of suspicious diabetes would be made if the two-hour value is over 120 mg. per cent and the three-hour result exceeds 110 mg. per cent. The criteria for interpretation by the Folin-Wu method is about 10-15 mg. per cent higher.

In the present era, the importance of tracking down the hidden diabetic in the general population, as well as in cases of pregnancy, has stimulated interest in devising extremely sensitive tests for this purpose. One described by J. W. Conn and others is the glucose-cortisone tolerance test.[11] If this approach is to be used, it should be employed between pregnancies. Another is the tolbutamide tolerance test using this drug intravenously.[12] It appears that both tests have special merit in diabetes detection, but more time is required to determine when and how often they are needed, if the glucose tolerance test fails to pinpoint the diagnosis.

It must be borne in mind that a glucose tolerance curve may be normal during the first trimester of pregnancy, but that a diabetic curve may emerge as pregnancy advances under the influence of increased glucocorticoid production.[13] A normally functioning pancreas may overcome the diabetogenic action of increased steroid production, whereas the one with the inherent defect, although well compensated in the nonpregnant state may become decompensated during pregnancy and evidence of abnormal carbohydrate tolerance results. This is amply substantiated by the work of Cobley and Lancaster,[14] who performed serial glucose tolerance tests at monthly intervals on 158 normal patients from the inception of pregnancy. They found that the glucose tolerance curves were similar in all trimesters, that hyperglycemia did not occur and that the curve returned to normal in three hours.

In spite of the fact that we all agree on the importance of recognizing and treating the frank diabetic pregnant patient, the problem as concerns the unsuspected diabetic in pregnancy is still unsettled. Definite criteria for its diagnosis agreeable to all investigators have not as yet been established.

There are two pitfalls to be guarded against: (1) the erroneous diagnosis of diabetes. This may lead to emotional trauma to the patient and unnecessary obstretrical interference; (2) inadequate treatment when it does exist. This is conducive to increased fetal wastage.

Diabetes detected merely by laboratory evidence should not be regarded as innocuous during pregnancy. The same care and supervision as applied to the frank diabetic must be given these patients, to increase the chances of a better fetal end result. This condition may remain relatively static and diet alone may suffice. On the other hand, the status may change and insulin therapy may be required. Failure to adapt therapy to the changing status may result in a poor fetal outcome. The need for insulin therapy may be determined by symptomatology, urinary findings and periodic postprandial blood sugar determinations. It must be realized that some of the unsuspected diabetics will progress to frank diabetes during the course of pregnancy. All patients with abnormal curves should test their urines daily for sugar and acetone.

The time and method of delivery of the patient with the abnormal glucose tolerance test are dependent upon the past obstetrical history and the current pregnancy. Premature delivery by the abdominal or vaginal route fourteen to twenty-one days prior to the estimated date of confinement is indicated in all patients with a poor obstetrical history, those with recurrent episodes of acidosis, polyhydramnios, or in those in whom a roentgenogram of the abdomen reveals a marked halo around the fetal skull. If pre-eclampsia develops, delivery should be effected within seventy-two hours of its recognition. In the uncomplicated case, labor may be induced whenever the cervix is favorable, or the onset of spontaneous labor may be awaited.

What is the outlook for the patient with the abnormal glucose tolerance curve during pregnancy? There are insufficient data at present to enable one to predict the answer. Some will become frank diabetics as pregnancy advances or shortly thereafter. In others the abnormal glucose tolerance curve will persist following delivery. However, in the vast majority the curve returns to normal during the puerperium, only to show a recurrence of disturbed carbohydrate metabolism under the stress of subsequent pregnancies. The interval of time that must elapse before these patients develop clinical diabetes is not definitely known. In a few, we have seen diabetes develop in from one to seven years, following the first abnormal glucose tolerance curve during pregnancy. Sufficient long-term follow-up studies are necessary before one can state with any degree of accuracy what percentage of these patients will become overt diabetics. It is conceivable that with sufficient longevity, the disease might become manifest in all of them.

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BOOK REVIEW

METHODS OF BIOCHEMICAL ANALYSIS. *Vol. 7, edited by David Glick. $9.50, pp. 363, 37 illus., 14 tables, Interscience Publishers, Inc., New York, 1959.*

This is the seventh volume of the excellent annual reviews dealing with methods of biochemical analysis, particularly in fields which are rapidly developing. This volume, like its predecessors, has maintained a high standard of excellence both in presentation and critical analysis. The subjects dealt with are: (1) "Immuno-electrophoretic Analyses," by Pierre Grabar, Institut Pasteur, Paris. The methods outlined introduce the sensitive method of specific precipitation by antibodies for the detection of various proteins after electrophoretic separation. Immuno-electrophoretic analysis (IEA) is performed by subjecting a protein mixture admixed in a gel to electrophoresis. When sufficient dispersion is obtained immune serum is allowed to diffuse perpendicularly to the axis of migration. In consequence, insoluble antigen-antibody complexes appear and areas of precipitation become visible. After appropriate separation minute quantities of antigenic constitutents may be identified and quantitated. Full technical details of the methods are outlined. (2) "The Analysis of Basic Nitrogenous Compounds of Toxicological Importance," by A. S. Curry, Forensic Science Laboratory, Harrogate, Yorkshire. Methods are outlined employing appropriate extraction, electrophoretic, and other methods, for the specific identification, purification, and quantitation of a large number of alkaloidal and other basic nitrogenous compounds. (3) "The Determination of Inositol, Ethanolamine, and Serine in Lipides," by John M. McKibbin, State University of New York Medical Center, Syracuse, New York. This chapter deals with advanced methods for the separation and identification, and quantitation by chromatographic countercurrent extraction and other solvent fractionation technics of the synthetic phosphatides. (4) "The Assay of Lipoprotein Lipase in Vivo and in Vitro," by Edward D. Korn, National Heart Institute, Bethesda, Maryland. In 1943 Hahn demonstrated the appearance of lipoprotein lipase in blood following the injection of heparin. Since then the literature on this subject has become very extensive. The present chapter deals with various aspects of the subject including the effect of heparin on lipoproteins, the action of lipoprotein lipase in vitro, the preparation of lipoprotein lipase, and methods of assay. (6) "Determination of Creatinine and Related Guanidinium Compounds," by John F. Van Pilsum, University of Minnesota, Minneapolis, Minnesota. The guanidinium compounds are concerned in many metabolic reactions, particularly those involving muscle metabolism and kidney function. The present chapter deals with various aspects of the biochemistry of these compounds including creatinine, creatine, arginine, guanidinoacetic acid, guanidine and methyl guanidine. Methods of separation, purification, and identification are fully described. (7) "The Determination of Ethyl Alcohol in Blood and Tissues," by Frank Lundquist, University Institute of Forensic Medicine, Copenhagen, Denmark. The determination of alcohol in blood, tissues, saliva, and urine has forensic significance in many countries. The chapter outlines in detail various methods of quantitative determination of alcohol. (8) "Determination of Heparin," by Louis B. Jaques and Helen J. Bell, University of Saskatchewan, Saskatoon, Canada. Methods for the extraction, isolation and quantitative determination of this trace substance and its significance are given in detail.

The book contains an excellent author and subject index and, in addition, a cumulative author index for all seven volumes of this series.

George F. Stoney
1887-1959

Joseph T. Beardwood, Jr., M.D., Philadelphia

Dr. George F. Stoney died on Feb. 1, 1959. He was one of the original members of the American Diabetes Association at the time of its inception. Dr. Stoney was born in Cleveland, Ohio, in 1887 and graduated from Jefferson Medical College in 1910. He was a member of many societies, but his greatest interest was diabetes and the diabetic. He served for many years as chairman of the diabetes commission in the state of Pennsylvania. He led an unceasing fight for the proper care of the diabetic patient, was always eager to teach young physicians and others interested in the more modern concepts of diabetes care. He was particularly active in attempting to persuade industrial employers not to penalize a patient because of his disease and maintained that diabetes is no handicap to the individual in maintaining his proper place in society. For many years he was chairman of the department of medicine at the Hamot Hospital in Erie, Pennsylvania, and at the time of his death was a member of the Governor's Committee on Diabetes under the Secretary of Health of the Commonwealth of Pennsylvania. Dr. Stoney was among the first ten members of the American Diabetes Association and continued to be actively interested in the work of our association until his death.

Erich Grafe

1881-1958

Prof. Dr. Med. H. Reinwein, Kiel

Erich Grafe, Prof. Dr. Med. Dr. h. c., Director Emeritus of the Department of Medicine and Neurology of the University of Würzburg died on May 18, 1958. He had just finished the second edition of his fundamental work, *Diseases of Nutrition and Metabolism and their Management.* A long and productive life has come to an end.

Grafe grew up in the humanistic tradition of a German family of scientists. After completion of his medical education, he pursued postgraduate training in physiology and in hygiene at the University of Berlin under Prof. Thierfelder and Geheimrat Rubner. In 1906 he accepted an appointment as assistant in the Department of Medicine of the University of Heidelberg under Prof. L. Krehl, whose pathophysiologic approach began at that time to have a decisive impact on medical thinking and research. Grafe's numerous scientific publications from Heidelberg, Rostock, and Würzburg demonstrate the lasting influence of his teachers, Rubner and Krehl; the fruitful cooperation with men such as Warburg, Morawitz, von Weizsacker and Freund; and the intimate scientific contact with colleagues beyond the frontiers of Germany, particularly in the United States, such as Lusk, Benedict, Dubois and Joslin. His wide range of scientific interest and endeavor is evidenced both by his textbook on *The Pathologic Physiology of the Energy and Nutritional Metabolism in Man, (Die pathologische Physiologie des Gesamtstoff—und Kraftwechsels bei der Ernaehrung des Menschen)*, dedicated to Rubner and Krehl, and his comprehensive contributions to the *Handbooks of Biochemistry,* by Oppenheim, and to the *Normal and Pathologic Physiology* by Bethe and von Bergmann.

In 1911, when very little was yet known about the synthetic chemical processes within the living organism, Grafe began his investigations on the effect of ammonium salts upon the nitrogen equilibrium, experiments which found confirmation later by R. Schoenheimer's early work with isotopes. The concept of a deranged metabolic pathway of carbohydrates in diabetes mellitus initiated Grafe's studies on the effect and the utilization of starch, caramels, levo-glucosanes, levulose, sorbitol and pentose, and on the role of exercise upon the metabolism in diabetes. With Fischler, Freund, von Redwitz and Strieck, he performed experiments on the influence of the central nervous system upon the energy and nitrogen metabolism of higher animals. These were prompted by the working hypothesis that the harmonious and simultaneous occurrence of metabolic processes in the living organism requires certain regulatory mechanisms. They were carried out with his Universal-respiration-apparatus developed in 1909.

After moving to the University of Rostock in 1922, where he had become the Director of the Medical Polyclinic, he turned to studies on the metabolism of tissue slices, using Warburg's technic. Some results of these studies were the observations that isolated tissue did not show any organ-specific metabolic characteristics, and that insulin was capable of increasing the O_2 uptake of the isolated diaphragm of the rat (Paasch, Reinwein and Singer).

In Würzburg (1926-1945), Grafe stimulated his associates in the study of the influence of the central nervous system on immune processes (Bogendorfer) and the metabolic changes induced by stimulation or destruction of the hypothalamus (Gruenthal, Mulholland and Strieck). A diabetes-like state was produced in the dog by circumscribed damage in the midbrain area. The radiation loss, the mean radiation temperature, and the specific density of man were examined with newly developed methods (Bohnenkamp), the mechanism of the specific dynamic action of protein was investigated (Oberdisse), and it was demonstrated that the active phase of muscle contraction rests in an osmodynamic rather than in a chemodynamic process (Fleckenstein). It gave Grafe a special satisfaction when he and Meythaler succeeded in demonstrating by injections of glucose solutions into the pancreaticoduodenal vein that hyperglycemia is an adequate stimulus for insulin secretion.

In 1926 Grafe developed a modern diet-study kitchen, having recognized the importance of dietetics through his numerous studies on the "luxus consumption." Following the example of the Deaconess Hospital in Boston, he then founded a "Fürsorgestelle" for diabetics, hoping in this way to contribute to the better care of the diabetic and to a decrease of diabetes mortality.

Grafe, as the director of a large university department, was constantly interested in supporting and stimulating investigations in the wide field of internal medicine. Deeply engaged as he was in teaching and his own investigations, he encouraged his associates to follow their own research interests. Basically he was a kind and friendly man, but he was forceful, unbending and uncompromising in his work. In his critique he could be sharp and stern, as witness his chapter on diabetes mellitus in the *Handbook of Internal Medicine.*

Foreign scientists frequently came to work with him in his clinical department and his laboratories, among them Harry E. C. Wilson of Glasgow, Andrew Ura of Valladolid, Alexander Marble of Boston, and Henry B. Mulholland of Virginia.

Grafe was an honorary member of many scientific societies; he received an honorary degree from the University of Rostock; he was the recipient of the Rienecker medal, and was slated to be the Honorary President of the 1958 Congress of the International Diabetes Federation. Internal medicine in Germany has lost with him one of the last representatives of the great school of pathophysiology of metabolism and nutrition.

We are indebted to Dr. Martin G. Goldner for his translation from the German.

ABSTRACTS

Bothe, Frederick A. (Abington Memorial Hosp., Philadelphia, Pa.): SURGICAL PROCEDURES IN THE DIABETIC PATIENT. Postgrad. Med. *25*:437-42, April 1959.

Surgery in diabetes is discussed from extensive clinical experience, and an analysis made of 1,300 surgical procedures in 5,000 patient admissions in four large Pennsylvania hospitals from 1950 to 1956. The abdominal pain in diabetic acidosis, the milder clinical features of acute surgical diseases in diabetics and peripheral vascular problems are discussed in detail. The presence of an extensive block in the posterior tibial artery and inadequate collateral circulation in gangrene of the heel of diabetics is an important finding arising out of injection studies of the blood vessels of amputated legs. S.B.B.

Burt, Richard L. (Dept. Obst. & Gynec., Bowman Gray School of Med., Wake Forrest College, Winston-Salem, N. C.): FURTHER OBSERVATIONS ON REACTIVITY TO INSULIN IN NORMAL PREGNACY. Obst. & Gynec. *13*:433-36, April 1959.

Normal subjects between thirty-six and forty weeks of gestation were studied after fasting fifteen to eighteen hours, and under basal conditions 0.1 U. of regular insulin per kilogram body weight injected intravenously. Blood samples were taken between five and sixty minutes. The hypoglycemia which developed in pregnant women was considerably less than in the nonpregnant. In addition to this insulin resistance late in pregnancy there was a decrease of amino nitrogen. This hypoamino-acidemia was mild when compared with tolbutamine which produces an exaggerated amino nitrogen depression late in pregnancy. C.A.V.

Christensen, P. J. (Biochemical Inst., Aarhus University, Aarhus, Denmark): TUBULAR REABSORPTION OF GLUCOSE DURING PREGNANCY. Scandinav. J. Clin. & Lab. Invest. *10*:364-71, 1958.

The renal threshold and tubular reabsorption of glucose have been investigated in five normal nonpregnant women, five normal women in the third and fourth months of pregnancy, two normal women in the seventh and ninth months of pregnancy, respectively, and one woman with renal diabetes in the first month of pregnancy. In the third and fourth months of pregnancy the renal threshold for glucose was decreased corresponding to an elevation of the glomerular filtration rate, indicating that the tubular threshold was unchanged. No difference in tubular reabsorptive capacity between the pregnant and the nonpregnant subjects was observed. G.A.W.

Christensen, P. J.; and Steenstrup, O. R. (Biochem. Inst. and Dept. of Obstetrics and Gynecology, Aarhus Univ., Denmark): URIC ACID EXCRETION WITH INCREASING PLASMA GLUCOSE CONCENTRATION (PREGNANT AND NON-PREGNANT CASES). Scandinav. J. Clin. & Lab. Invest. *10*:182-85, 1958.

The uric acid clearance and glomerular filtration rate (insulin clearance) have been determined in three normal pregnant and three normal nonpregnant women both in the fasting state and with increasing plasma glucose concentration. The uric acid clearance is elevated in pregnancy, but not significantly more than that corresponding to the increase in glomerular filtration rate. An approximately linear relationship was observed between uric acid excretion and plasma glucose concentration, the latter ranging from normal fasting levels to beyond the level of complete saturation of the renal tubules, with glucose. Pregnancy introduced no difference in the tubular handling of glucose. G.A.W.

Christophe, Jean; and Mayer, Jean (Dept. of Nutrition, Harvard Sch. of Pub. Health, Boston, Mass.): EFFECTS OF ACUTE AND CHRONIC TREATMENTS WITH CARBUTAMIDE (BZ-55) ON OBESE—HYPERGLYCEMIC MICE AND THEIR LEAN LITTERMATES. Endocrinology *64*:664-70, May 1959.

Carbutamide was fed to both obese-hyperglycemic mice and their lean litter mates over a seven-week period. The blood sugar level of the latter was increased and of the former unchanged by this treatment. Food intake and weight increases were not significantly affected.

At the end of the chronic experiment all animals were given a single subcutaneous injection of carbutamide. Of those animals never receiving carbutamide before, the lean ones showed a drop in blood sugar while the obese ones showed an inconsistent rise. On the other hand, the lean and the obese mice chronically treated with carbutamide showed no change in blood sugar in response to the single injection. The lean, carbutamide-treated mice exhibited an increased hyperglycemic response to glucagon and ACTH. R.L.J.

Covian, Miguel R.; Migliorini, Renato H.; and Berezin, Abrahao (Dept. of Physiol., Sch. of Med. of Ribeirao Preto, Ribeirao Preto, Sao Paulo, Brazil): CARBOHYDRATE METABOLISM IN HEMIDECORTICATE RATS. Metabolism 7:717-22, November 1958.

Sixty per cent of hemidecorticate male rats showed impaired tolerance to glucose fed by stomach tube and 46 per cent when fed intravenously. Twenty-five per cent of the hemidecorticate female rats showed a decreased tolerance to glucose when given through a stomach tube and 56 per cent when given intravenously. Insulin sensitivity was diminished in both sexes. The author suggests that impaired homeostatic control of carbohydrate metabolism in these experimental animals can be explained on an alteration of hormonal balance. The impaired insulin carbohydrate metabolism persisted for three to four months after the operation. R.W.S.

Craig, Carol E.; Calvin, James L.; and McNeal, E. R. (Mount Holyoke College, South Hadley, Mass.; Dept. of Med., Cardiology Clin., Youngstown Hosp., Youngstown, O.): THE EFFECTS OF ORINASE IN CLINICAL DIABETES. Ohio M. J. *54*:1441-43, November 1958.

The authors present their experiences in the treatment of thirty diabetic patients with Orinase. G.J.H.

Creutzfeldt, Werner; Kümmerle, Fritz; and Kern, Ernst (Depts. of Medicine and Surgery, University of Freiburg, Germany): OBSERVATIONS IN FOUR CASES OF TOTAL DUODENO-PANCREATECTOMY FOR CARCINOMA OF THE PANCREAS. Deutsche med. Wchnschr. *84*:541-49, March 20, 1959.

Three of the four patients who underwent total pancreatectomy suffered from carcinoma of the pancreatic head, one from carcinoma of the papilla Vateri. One died twenty-four hours

postoperatively, the three others were alive fourteen, eleven and two months after the operation. All patients developed hyperglycemia and glycosuria within a few hours after surgery; all showed great insulin sensitivity. Their diabetes could be controlled at a diet of 200-250 gm. KOH/day with a daily insulin dose of less than 40 U. This basic insulin requirement rose to about 70 U. in one of these patients during an intercurrent infection. In spite of the great insulin sensitivity and low insulin requirement, the surgical diabetes in man is not to be considered as a "mild" diabetes. Insulin withholding caused immediate aggravation of the disease and development of acidosis within two days. Reestablishment of control was surprisingly easy since the insulin sensitivity persisted even in the acidotic phase. The authors question whether this might be due to the absence of glucagon in this type of diabetes, or to the absence of a complicating disease, which usually is responsible for the development of ketoacidosis. Liver tests and laparoscopic inspections of the liver did not give evidence of the development of fatty degeneration, which in the dog occurs usually and rapidly after total pancreatectomy.

Attempts to substitute tolbutamide for all or part of the daily insulin dose failed. Tolbutamide did not seem to potentiate the effect of insulin. Phenethyldiguanid, on the other hand, could be substituted satisfactorily for part of the insulin requirement. If insulin was withheld completely phenethyldiguanid delayed the diabetic decompensation, but could not prevent it. The authors describe in detail the indications for pancreatectomy, the signs and symptoms of pancreatic carcinoma, the postoperative management and the endocrine and exocrine substitution therapy. If the ensuing diabetes is properly controlled, pancreatectomy is tolerated fairly well and is not accompanied by serious defects. M.G.G.

Date, J. W. (Inst. of Hygiene and of Biochem., Univ. of Aarhus, Aarhus, Denmark): A QUANTITATIVE METHOD FOR ESTIMATION OF SOME CARBOHYDRATES ON FILTER PAPER. Scandinav. J. Clin. & Lab. Invest. *10*:149-54, 1958.

A method for the quantitative determination of glucose, galactose, xylose and arabinose on paper chromatograms is described. The sugars are treated *on* the paper with an aniline-citric acid reagent, eluted, and the optical density is read in a spectrophotometer at 420 m. Recoveries of these carbohydrates from solutions of sodium acetate buffer ranged between 92 and 101 per cent. G.A.W.

Date, J. W. (Inst. of Hygiene and of Biochem., Univ. of Aarhus, Aarhus, Denmark): QUANTITATIVE DETERMINATIONS OF SOME CARBOHYDRATES IN NORMAL URINE. Scandinav. J. Clin. & Lab. Invest. *10*:155-62, 1958.

The carbohydrate excretion in twenty-four-hour urine collections from five normal young men and five normal young women was examined by help of two-dimensional paper chromatography. Quantitative values for glucose, galactose, lactose, xylose and arabinose, which were present in all the urine collections investigated, were obtained by a colorimetric method. Glucose was excreted in higher amounts than any of the other carbohydrates. More xylose and arabinose were excreted in urine than lactose. Only small amounts of galactose were generally present in urine.

Only small variations were found in the excretion of the carbohydrates when one person was given the same diet for three twenty-four-hour periods. During fasting the excretion of all the carbohydrates investigated decreased considerably. G.A.W.

Douthwaite, A. H. (Correspondence) (London, W. 1, England): GLUCOSE. Brit. M. J. *1*:646, March 7, 1959.

The author expresses his concern about the possibility of condemnation of glucose or liquid glucose in therapeutics by the Food Standards Committee in his country. C.A.R.

Ellenberg, Max (Mount Sinai Hosp., New York, N.Y.): DIABETIC NEUROPATHY PRESENTING AS THE INITIAL CLINICAL MANIFESTATION OF DIABETES. Ann. Int. Med. *49*:620-31, September 1958.

1. Representative cases are reported to indicate that diabetic neuropathy may be the initial clinical manifestation of diabetes. 2. Awareness of this occurrence and its diagnostic application should help resolve some hitherto obscure clinical problems. 3. Diabetic neuropathy should be regarded as a concomitant and integral feature of diabetes mellitus, rather than as a complication of the disease. W.R.K.

Farquhar, James F.; and Sklaroff, Stanley A. (Dept. of Child Life and Health, and of Public Health and Social Medicine, Univ. of Edinburgh, Scotland): THE POSTNATAL WEIGHT LOSS OF BABIES BORN TO DIABETIC AND NONDIABETIC WOMEN. Arch. Dis. Childhood *33*:323-29, August 1958.

The authors investigate the claim that infants of diabetic mothers are heavier than normal due to edema, and that such infants lose more weight than normal babies postnatally due to water loss. They present the method of weighing and nursing care and results of a comparative study of postnatal changes in weight in thirty-one fed babies of diabetic mothers delivered by cesarean section, twenty-nine unfed babies of diabetic mothers born by cesarean section matched as far as possible for maternal age and parity with sixty nondiabetic cesarean controls and sixty normal spontaneous deliveries. Weight change was considered both relatively as a percentage of birth weight and in absolute terms. No association between percentage weight and birth weight was found on any day examined, from zero to fourteen days (the least such variability occurring at the third day or fourth day and increasing thereafter). The infants of diabetic mothers subjected to prolonged fluid deprivation lost more weight than when fluids were given early, and also lost more weight than control infants delivered either vaginally or by cesarean section. Infants of either group lose more weight over a longer period than infants delivered spontaneously to nondiabetic women, and also regain weight more slowly. R.L.J.

Felts, John H.; Meschan, I.; and Oddie, T. H. (Dept. of Med. & Radiology, Bowman Gray School of Med., Wake Forest College & the North Carolina Baptist Hosp., Winston-Salem, N.C.): ASSAY OF THYROID FUNCTION IN DIABETES MELLITUS. J. Clin. Endocrinol. *19*:330-33, March 1959.

Thyroid function was assayed in twenty-five unselected patients with diabetes mellitus by measuring thyroidal and renal clearance rates of I^{131}. The thyroidal clearance rate of I^{131} was within the normal range in all patients. The renal clearance rate was markedly decreased in patients with intercapillary glomerulosclerosis as is to be expected, but was within normal limits in the other diabetic subjects including two with diabetic retinopathy without nephropathy. This indicates that thyroidal handling of iodine is normal in all phases of diabetes mellitus, and that altered urinary excretion patterns are a reflection of the renal lesions rather than of the underlying systemic disease. G.J.H.

Garland, Hugh (The General Infirmary, Leeds, England): ENDOGENOUS HYPOGLYCAEMIA. Proc. Roy. Soc. Med. *51*:979-90, December 1958.

This well-documented and informative presidential address is written from the neurological point of view. Apart from the incidental finding of low blood sugar levels in such disorders as Addison's disease, hypopituitarism or gross liver damage, endogenous hypoglycemia is considered under the headings of organic hyperinsulinism, complications of gastric surgery, and cases which are predominantly psychosomatic in origin. Neurological manifestations which accompany hypoglycemia receive special consideration. The need for a more precise definition of the term "hypoglycemia" is considered, with particular reference paid to the methods used for blood sugar determinations. G.A.W.

Giles, Kenneth M.; and Harris, John E. (John E. Weeks Memorial Lab., Dept. of Ophthalmology, Univ. of Oregon Med. Sch., Portland, Ore.): RADIOELECTROPHORETIC PATTERNS OF AQUEOUS AND PLASMA: AFTER INTRAVENOUS INJECTION OF I^{131}-LABELED INSULIN INTO RABBITS. Am. J. Ophth. *46*:196-204, Part II, November 1958.

This study concerns the movement of glucose between aqueous and plasma within the orbit. It is known that glucose moves into the lens by some process other than simple diffusion. The purpose of this paper is to determine the influence of insulin on such movement.

Following the intravenous administration of I^{131} labeled insulin to normal, diabetic, and hyperglycemic normal rabbits, a number of findings were observed. The trichloroacetic acid precipitable activity in the plasma decreased rapidly after the injection. This activity rose to a peak in the aqueous and then fell to low levels. Similar patterns of radioelectrophoretograms were obtained from both aqueous and plasma from normal, hyperglycemic normal, and diabetic rabbits. Only a small fraction of biologically active insulin was found in the aqueous. The principal conclusions are that insulin does not enter the aqueous in a significant amount. Neither does it appear to cross the blood-retinal barrier. It is thus not surprising that the retinopathy of diabetics is unrelated to insulin requirement. R.W.S.

Goodman, Joseph I. (Diabetic Clin., Mt. Sinai Hosp., Cleveland Heights, Ohio): OBJECTIVES OF EFFECTIVE DIABETIC MANAGEMENT. Ohio M. J. *54*:144-48, November 1958.

The author presents a very well written clinical discussion of reasonable aims to be pursued in the management of clinical diabetes mellitus. G.J.H.

Grant, W. C.; and Fahrenbach, M. J. (American Cyanamid Co., Pearl River, N.Y.): EFFECT OF DIETARY SUCROSE AND GLUCOSE ON PLASMA CHOLESTEROL IN CHICKS AND RABBITS. Proc. Soc. Exper. Biol. & Med. *100*:250-52, February 1959.

The authors present data to support the conclusion that serum cholesterol values of rabbits fed a cholesterol diet containing sucrose were higher than those from a group on a similar diet containing glucose. However, there was no difference in plasma cholesterol when either glucose or sucrose was fed without adding cholesterol. It is suggested that a possible mechanism for this is that sucrose favors absorption of exogenous cholesterol, but there is no other evidence presented for this. G.J.H.

Hamwi, George J.; and Serbin, Richard A. (Dept. of Med., Div. of Endocrinology and Metabolism, The Ohio State Univ., Columbus, Ohio): TOLBUTAMIDE: A REVIEW OF ITS MECHANISM AND ITS ROLE IN CLINICAL PRACTICE. Ohio M. J. *54*:1437-40, November 1958.

The authors review the literature in regard to the mode of action of the sulfonylurea group of compounds, and present their clinical experiences in a series of 258 patients. The selection of patients, the incidence of responsiveness and the complications reported are similar to previous reports. G.J.H.

Hayles, Alvin B.; and Power, Marschelle H. (Sec. of Pediatrics & Sec. of Biochemistry, Mayo Clinic & Mayo Foundation, Rochester, Minn.): FAILURE OF INSULIN TO INDUCE A CHANGE IN RATE OF GROWTH IN A FOURTEEN-YEAR-OLD BOY WITH ANTERIOR PITUITARY INSUFFICIENCY. J. Clin. Endocrinol. *19*:248-51, February 1959.

The administration of insulin in a dose of 60 U. daily in combination with desiccated thyroid, ¾ gr., and cortisone 15 mg. daily for a period of eight months failed to produce a change in the rate of growth of a fourteen-year-old boy with anterior pituitary insufficiency and dwarfism. This work was performed following the report in 1953 of Salter and Best who demonstrated significant growth in hypophysectomized rats following the administration of insulin. Although the patient reported gained weight during the period of insulin administration, there were no significant changes in the nitrogen, calcium, phosphorus, and potassium balances during the treatment period as compared with the control period. G.J.H.

Hennes, Allen R.; and Shreeve, Walton W. (Med. Dept., Brookhaven Nat'l. Lab., Upton, L.I., N.Y.): HORMONAL EFFECTS ON C^{14} ACETATE METABOLISM IN THE HUMAN. Proc. Soc. Exper. Biol. & Med. *100*:246-50, February 1959.

The data presented by these authors suggest the following tentative conclusions. (1) Adrenal 17-hydroxycorticoids appear to exert an effect on utilization of acetate and to decrease oxidation of this two-carbon fragment to CO_2. (2) In the human, the carboxyl carbon of the acetate molecule is more readily oxidized than is methyl carbon. There is also evidence to suggest that the carboxyl carbon of the acetate molecule may also be used preferentially for lipid synthesis in the human. (3) The syndrome of lipoatrophic diabetes appears to be associated with a decreased ability to store and possibility to synthesize lipids in the adipose tissue rather than due to an increase in utilization of lipids of adipose tissue. (4) The stable adult diabetic may have a defect in conversion of two-carbon fragments to fatty acids, even when the fasting blood sugar is normal. G.J.H.

Herman, Joseph B. (Diabetic Clinic, Groote Schuur Hosp. & Dept. of Med., Univ. of Cape Town, South Africa): GOUT AND DIABETES. Metabolism 7:703-06, November 1958.

Eighty-two ambulant gouty patients and twenty-seven non-gouty arthritic patients were subjected to carbohydrate metabolism studies. Impaired carbohydrate tolerance was found in a high percentage of the gouty subjects. The author concludes that some factor specifically related to gout must be responsible for the abnormal carbohydrate metabolism. The intermediary products of nucleoprotein breakdown resulting from the disturbance of metabolism in gout may act as a diabetogenic agent. The author suggests that since alloxan resembles uric acid a substance similar to alloxan may occur as a result of nucleoprotein breakdown. R.W.S.

Heycock, J. B.; and Wilson, J. (Sutherland Children's Hosp. and Dept. of Neurol. and Neuro-Surgery, Royal Victoria Infirmary, Newcastle-upon-Tyne, Northumberland, England): DIABETES MELLITUS IN A CHILD SHOWING FEATURES OF REFSUM'S SYNDROME. Arch. Dis. Childhood *33*:320-22, August 1958.

This paper describes a diabetic child showing most of the features of a condition described by Refsum under the name of heredopathia atactica polyneuritiformis. The malady is thought to be a recessive condition and is usually referred to as Refsum's syndrome. Only six other cases have so far been reported, and no case has previously been described of this syndrome in association with diabetes mellitus.

The salient features of heredopathia atactica polyneuritiformis are: (1) Atypical retinitis pigmentosa with hemeralopia and concentric constriction of visual fields. (2) A picture of chronic polyneuritis with progressive pareses of distal parts of limbs and decreased or absent reflexes. (3) Ataxia and other cerebellar signs. (4) Increased cerebrospinal fluid protein with normal cell count. (5) In some cases abnormal electrocardiographic changes have been noted, in others neurogenic hearing loss, pupillary abnormalities and skin changes resembling ichthyosis.

The condition of the child we have described resembles Refsum's syndrome although there are several unusual characteristics, chiefly, photophobia rather than night blindness and the presence of dysarthria.

In the patient the relationship between the diabetes mellitus and the degenerative condition of the central nervous system was obscure. The clinical picture was quite distinct from that of diabetic myelopathy (Garland and Taverner, 1953). Although the cerebrospinal fluid protein is elevated in both conditions, our patient's disease was insidiously progressive and quite unaffected by control of the diabetes. The family history suggests that the diabetes may have been independent. W.R.K.

Hungerford, Gerald F. (Dept. of Anatomy, Univ. of S. California, Los Angeles, Calif.): EFFECT OF ADRENALECTOMY AND HYDROCORTISONE ON LYMPH GLUCOSE IN RATS. Proc. Soc. Exper. Biol. & Med. *100*:754-56, April 1959.

The author confirms the fact that in the fasted state lymph glucose is in equilibrium with blood plasma glucose, probably at the capillary level. Less than 0.3 per cent of absorbed glucose appears in the lymphatic stream. The greater quantity of glucose which enters the blood capillaries in normal fasted rats is explained on the basis of difference in rates of blood flow and lymph formation rather than endothelial selectivity. Plasma and lymph glucose values are low in adrenalectomized rats but are returned toward normal by pretreatment with hydrocortisone. Lymph flow in hydrocortisone pretreated rats is increased by 100 per cent after gavage of glucose solution but not after water gavage. G.J.H.

Introzzi, P.; Bernasconi, C.; and Buscarini, L. (Med. Clin. of the University of Pavia, Italy): SERUM PROTEINS, LIPIDS AND PROTEIN-BOUND CARBOHYDRATES IN VASCULAR COMPLICATIONS OF DIABETES MELLITUS. Acta med. Scandinav. *160*:47-58, Jan. 31, 1958.

Serum proteins, lipids and protein-bound carbohydrates were analyzed in thirty-five diabetics with evidence of atherosclerosis and in twenty-six diabetics without signs of atherosclerosis. The gamma globulin level was increased significantly in both groups. Only in the diabetics with atherosclerosis did the concentration of albumin decrease and the beta globulin increase with any significance. Total lipids, total cholesterol, cholesterol, cholesterol/phospholipids ratio increased and esterified cholesterol/total cholesterol ratio decreased in the serum of diabetics without atherosclerosis and in the serum of diabetics with atherosclerosis. Both groups presented an increase on the beta lipoprotein with an elevation of its content of free cholesterol. Serum protein-bound hexose, hexosamine and sialic acid showed similar and significant increase only in the group of diabetics with atherosclerosis. In the same group, the distribution of the glycoproteins in the electrophoretic pattern revealed a significant increase in the alpha-2-globulin-bound carbohydrates with a significant rise in the alpha-2-globulin-bound carbohydrates/alpha-2-globulin ratio. In the other fractions the changes of the carbohydrates were always almost equal to those of the proteins. B.F.K.

Jackson, Robert L. (University of Missouri, Sch. of Med., Columbia, Mo.): NUTRITIONAL MANAGEMENT OF CHILDREN WITH DIABETES MELLITUS. J.A.M.A. *168*:42-46, Sept. 6, 1958.

Dietary management is of major importance in the treatment of children with diabetes, as the nature and severity of the disease are such that insulin therapy is required. In addition to the use of a nutritionally adequate diet, food must be given in the proper relationship to the distribution of insulin and to changes in the patient's physical activity.

The ultimate success of any diabetic regimen will depend on the thorough education of the child and his parents so that they become independent and competent in their abilities to manage the disease. Instruction, therefore, must be simple and straightforward and vary according to the ability of the parents and the child to learn. By using this philosophy of dietary and diabetic management, the child with diabetes can be happy and well adjusted. He need not lead a regimented life but, instead, a flexible, normal life which permits control of the disease and delays or prevents the development of degenerative changes. B.F.K.

John, Henry J. (St. Luke's Hosp., Cleveland, Ohio): SOME INTERESTING OBSERVATIONS IN DIABETES MELLITUS. Ohio M. J. *54*:1449-51, November 1958.

The author presents ten patients each of whom illustrates a phase in the management of diabetes which has presented difficulty to physicians. These include such things as hypoglycemia without symptoms, infection as the precipitating cause of diabetes, decrease of blood sugar without insulin, cases of delayed onset of diabetes, and mistaken diagnoses. G.J.H.

Johnson, R. E.; Sargent, F., II; and Passmore, R. (Depts. of Physiol., Univ. of Illinois, Urbana, Ill.; and Edinburgh University, Scotland): NORMAL VARIATIONS IN TOTAL KETONE BODIES IN SERUM AND URINE OF HEALTHY YOUNG MEN. Quart. J. Exper. Physiol. *43*:339-44, October 1958.

To establish normal values and ranges for studies of ketosis, total ketone bodies have been estimated in the urine and serum of 208 healthy young men, eating nonketogenic adequate diets and engaged in moderate daily physical activity. Under standardized postabsorptive conditions timed specimens of urine were collected, and venous blood was drawn. The urinary excretion rate of ketone bodies differed significantly in summer and winter. In hot weather the mean rate was 0.9 μ-mole/min.; in cold weather it was 2.8 μ-mole/min.; in cool weather it was 1.7 μ-mole/min. For serum, regardless of season, the mean was 0.7 m-mole/L. If two standard deviations be taken as the normal

range, it is suggested that for most conditions the upper limit of normal for serum be considered as 1.4 m-mole/L. and for urine 5 μ-mole/min. G.A.W.

Johnston, Dewey W. (Ft. Worth, Tex.): ERUPTIVE XANTHOMAS IN DIABETES MELLITUS. Texas J. Med. 55:50-54, January 1959.

A case of eruptive xanthomatosis in a young girl twelve years of age has been reviewed. The lesions disappeared after six weeks of insulin and diet therapy. The metabolic pathways and derangements involved have been emphasized. B.F.K.

Kerby, Gerald R. (University of Kansas, Sch. of Medicine; now at U.S. Naval Hosp., Bethesda, Md.): DIABETES: THE SEARCH FOR THE ANTIDIABETIC HORMONE. J. Kansas M. Soc. 60:35-38, January 1959.

A thesis written when the author was a senior medical student at the University of Kansas School of Medicine is a well documented historical review of the search for the antidiabetic hormone. B.P.K.

Kesson, C. W. (St. George's Hosp., London, England): DIABETES MELLITUS IN CHILDHOOD. Practitioner *182*:314-19, March 1959.

A discussion of the incidence, etiology, clinical manifestations, diagnosis, and treatment of the juvenile diabetic. W.R.K.

Kipnis, David M.; Helmreich, Ernst; and Cori, Carl F. (Dept. of Biological Chemistry, Washington University School of Medicine, St. Louis, Mo.): STUDIES OF TISSUE PERMEABILITY. IV. THE DISTRIBUTION OF GLUCOSE BETWEEN PLASMA AND MUSCLE. J. Biol. Chem. *234*:165-70, January 1959.

Distribution of free glucose was measured in rat diaphragm and gastrocnemius and extracellular volume was estimated by raffinose space. Alloxan diabetes eliminated intracellular muscle glucose and insulin administration replaced it once more. Adrenalectomy caused a decrease in extracellular glucose which failed to return upon treatment with glucose or glucose and insulin. Epinephrine injection, also fasting plus hyperglycemia, produced an accumulation of glucose within the muscle cell. Results indicate that the rate of glucose metabolism in muscle cells is limited by factors other than muscle permeability. A.R.C., JR.

Lacy, Paul E.; and Davies, J. (Washington University School of Medicine, St. Louis, Mo.): DEMONSTRATION OF INSULIN IN MAMMALIAN PANCREAS BY THE FLUORESCENT ANTIBODY METHOD. Stain Technology *34*:85-89, March 1959.

Fluorescein isocyanate anti-insulin globulin was used to stain beta cells selectively in sectioned pancreatic tissue. Technical details are emphasized. W.R.K.

Lawrence, R. D. (Correspondence) (London, W. 1, England): POISONING BY TOLBUTAMIDE. Brit. M. J. *1*:644, March 7, 1959.

The author reports briefly a patient who reacted unfavorably to tolbutamide administration, with development of symptoms and signs of "liver decompensation." The condition reverted to normal following the cessation of tolbutamide. C.A.R.

Lipscomb, Harry; Dobson, Harold L.; and Greene, James A. (Dept. of Medicine, Baylor University Coll. of Med., Houston, Tex.): INFECTION IN THE DIABETIC. South. M. J. 52:16-23, January 1959.

The authors review experimental work and hypotheses advanced to explain the increased susceptibility of diabetics to infection; emphasize the tendency for infections in the diabetic to be bizarre, poorly localized and grave; and outline a method of management stressing precise localization of the infection, adequate debridement or drainage, judicious local measures, accurate bacteriologic diagnosis, antibacterial sensitivity studies, comprehensive antibacterial therapy and appropriate supportive measures. L.S.S.

McKendry, J. B. R.; Kuwayti, K.; and Rado, Peter P. (Metabolism Service, Ottawa Civic Hospital, Ottawa, Canada): CLINICAL EXPERIENCE WITH DBI (PHENFORMIN) IN THE MANAGEMENT OF DIABETES. Canad. M. A. J. *80*:773-78, May 15, 1959.

This is a report of the use of DBI in a series of fifty-eight diabetic patients, only seven of whom were under forty years of age. Of these, 60 per cent had a satisfactory hypoglycemic response as well as tolerance of the drug. Success was greater in the older patients with heavy body build and lesser insulin dosage. In successfully treated patients, DBI reduced insulin need by an average of 33 U. Some patients unsuccessfully treated by arylsulfonylureas (tolbutamide or carbutamide) could be successfully treated with DBI, as well as the reverse. When treatment was effected with DBI, whether alone or with insulin, regulation was smoother than on insulin alone. Illustrative case reports were given among which were adult patients in whom DBI was effective at dosage levels as low as 75 mg. per day. S.B.B.

Macy, Dorothy, Jr. (Philadelphia Gen. Hosp., Pa.): PROFOUND HYPOGLYCEMIA. J. Am. M. Women's A. *14*:226-28, March 1959.

A regimen for the treatment of profound hypoglycemia is outlined. Glucose is given at a minimum rate of 150 gm. per hour. Vitamins, potassium, and hydrocortisone are part of the routine management of patients with severe hypoglycemic reactions. W.R.K.

Mayo, Henry W., Jr.; and Enerson, Daniel M. (Dept. of Surgery, State University of New York Upstate Medical Center, Syracuse, N.Y.): ENDOCRINE INFLUENCES OF THE PANCREAS ON GASTRIC SECRETION. I. THE EFFECTS OF GLUCAGON AND ALLOXAN ON HEIDENHAIN POUCH SECRETION. Surgery *44*:91-98, July 1958.

Heidenhain (denervated) pouches were constructed in dogs and gastric juice collected hourly for five-hour periods. Intravenous injection of glucagon (300 to 600 μg.) produced a reduction in acid secretion. Glucagon is probably not concerned with the hormonal control of gastric secretion. Alloxan (60 to 75 mg. per kg. of body weight) produced an elevation in gastric secretion in diabetic animals. It is suggested that alloxan might abolish an islet cell hormone which normally inhibits gastric secretion. A.R.C., JR.

Meier, Hans; and Yerganian, George A. (Depts. of Pathology, The Children's Med. Center & Harvard Med. School, & The Children's Cancer Res. Foundation, Boston, Mass.): SPONTANEOUS HEREDITARY DIABETES MELLITUS IN CHINESE HAMSTER (*Cricetulus griseus*). I. PATHOLOGICAL FINDINGS. Proc. Soc. Exper. Biol. & Med. *100*:810-15, April 1959.

Although diabetes mellitus has been reported in a number of nonrodent species, including cattle, pigs, sheep, dogs and cats, the occurrence of spontaneous diabetes mellitus in laboratory rodents has apparently not been reported before. The authors of this paper present the pathologic findings in the Chinese hamster indicating the occurrence of spontaneous diabetes mellitus in which some evidence is presented that the

disease is genetically determined. The possible significance of these findings for intensive studies of the inheritance and other potential etiologic factors in the occurrence of diabetes mellitus in man is obvious, particularly since many of the pathologic findings were similar to those reported in humans. G.J.H.

Mirsky, I. Arthur; Gitelson, Simon; and Perisutti, Gladys (Dept. of Clin. Sci., Univ. of Pittsburgh, Sch. of Med., Pittsburgh, Pa.): THE EFFECT OF TOLBUTAMIDE ON THE DIABETOGENIC ACTION OF SOMATOTROPIN. Endocrinology *64*: 766-68, May 1959.

Administration of tolbutamide to dogs simultaneously with somatotropin prevents the expected diabetogenic effect of the latter. R.L.J.

Murdaugh, H. V., Jr.; Robinson, R. R.; and Doyle, E. M. (Dept. of Med., Duke Univ. Med. Center and the Med. Service V.A. Hosp., Durham, N.C.): THE MECHANISM OF INSULIN ANTIDIURESIS. J. Lab. & Clin. Med. *53*:569-71, April 1959.

These authors again confirm the antidiuresis that occurs in response to commercially available insulin in a very nicely conceived plan of clinical experiments. The probable mechanism of this antidiuresis is presented. The fact that antidiuresis was not obtained in a patient with diabetes insipidus and in normal subjects who had been given alcohol to inhibit antidiuretic hormone is presented as evidence that the insulin antidiuresis is mediated through the action of ADH, and is not due to a specific effect of insulin upon the renal tubule. G.J.H.

Murrell, L. R.; and Nace, Paul Foley (McMaster Univ., Hamilton, Ontario, Canada, and Marine Biological Lab., Woods Hole, Mass.): EXPERIMENTAL DIABETES IN THE CATFISH: NORMAL AND ALLOXAN-DIABETIC BLOOD GLUCOSE AND PANCREATIC HISTOLOGY. Endocrinology *64*:542-50, April 1959.

Administration of alloxan to catfish produced hyperglycemia accompanied by pancreatic beta cell degranulation, hydropic degeneration and nuclear disintegration. Use of this experimental animal in the study of alloxan diabetes is discussed. R.L.J.

Myhre, J. R. (Medical Dept. A, The University Hosp., Bergen, Norway): THE DIFFERENCE IN GLUCOSE CONTENT OF THE HEPATIC VENOUS BLOOD AND THE ARTERIAL BLOOD DURING BASAL CONDITIONS. Scandinav. J. Clin. & Lab. Invest. *11*:10-17, 1959.

Using hepatic venous catheterization together with the anthrone method for glucose determination, the arterial-hepatic venous glucose difference, D, was studied in twenty fasting human subjects by serial observation at ten-minute intervals for two hours. D varied from 3.8 to 18.5 mg. per cent, and was statistically significant in all cases. No statistically significant difference between the values obtained during the first and second hour of examination could be demonstrated. On the other hand considerable fluctuations were observed between individual values in the same subject. In twenty out of 218 pairs of determinations a slightly higher glucose content was recorded in the arterial than in the hepatic venous blood.

The results indicate that quantitative values for D can be determined providing that a sufficient number of observations are made. G.A.W.

Newcomb, Alvah; and Traisman, Howard S. (Dept. of Pediat., Northwestern Med. Sch., Children's Memorial Hosp., Chicago, & Evanston Hosp., Evanston, Ill.): EXPERIENCES WITH THE LENTE INSULINS IN DIABETIC CHILDREN. Illinois M. J. *115*:264-66, May 1959.

Thirty diabetic children chosen for study because of poor control of glycosuria and/or frequent hypoglycemia were treated with varying mixtures of the Lente insulins. Duration of diabetes ranged from one to eight and a half years. Diets were weighed, fractional urine tests recorded and blood drawn in the fasting state for glucose determination. An evaluation of the patient's well-being, freedom from symptoms, and normal weight gain was made. Twenty-two of the thirty children studied showed improvement on a combination of the Lente insulins suited to their individual need. R.L.J.

Osler, Mogens; and Pedersen, Jørgen (Letters to Editor) (Royal Maternity Dept. B, Copenhagen, Denmark): WEIGHT CHANGES IN INFANTS OF DIABETIC MOTHERS. Lancet *1*:474, Feb. 28, 1959.

The authors briefly discuss possible reasons for the increased weight of newborn infants of diabetic mothers. Their explanation is that the constantly high glucose supply during pregnancy augments the deposits of glycogen and fat in the fetus. Thus, the newborn infant is overweight, is fat, and has a relatively high intracellular water content in connection with glycogen. The newborn infant consumes first glycogen, the bound water is excreted, and this explains the great diuresis and weight loss. When the glycogen depots are nearly exhausted, fat is burned. During the whole time protein is broken down as necessary. C.A.R.

Passmore, R.; and Johnson, R. E. (Physiol. Dept., University of Edinburgh, Scotland): THE MODIFICATION OF POST-EXERCISE KETOSIS (THE COURTICE-DOUGLAS EFFECT) BY ENVIRONMENTAL TEMPERATURE AND WATER BALANCE. Quart. J. Exper. Physiol. *43*:352-61, October 1958.

The ketosis that may arise following a ten-mile walk in the postabsorptive state (the Courtice-Douglas effect) has been studied in ten young men. Each completed two walks followed by six hours of recovery. One experiment was in a warm environment (about 24° C.), the other in a cool environment (about 12° C.). During both measured amounts of water were given, sufficient to maintain a good flow of urine. For the previous two days an artificial diet was eaten, providing 3,000 cal./day (15 per cent from protein, 45 per cent from fat and 40 per cent from carbohydrate) and unlimited fluids. In all experiments, rates of excretion of total ketone bodies increased after the walk. If ketosis is defined as a ketonemia above 1-4 m-mole/L. of serum or a ketonuria above 5 μ-mole/min., then it developed in nine of the twenty experiments, six being in the cool environment. The greatest ketosis was observed when water balance was positive. It did not develop when there was a large negative water balance. The Courtice-Douglas effect appears to be a general metabolic phenomenon, whose magnitude may be modified by environmental temperature and by hydration, as well as previous diet. G.A.W.

Pearson, Carl M.; and Rimer, David G. (Dept. of Med., Univ. of California School of Med., Los Angeles, Calif.): EVIDENCE FOR DIRECT UTILIZATION OF FRUCTOSE IN WORKING MUSCLE IN MAN. Proc. Soc. Exper. Biol. & Med. *100*:671-72, April 1959.

The authors present data on the effect of infused fructose on work capacity of a young male subject with an unusual metabolic deficiency of striated muscle in which there was a failure to form lactic acid under anaerobic conditions. The defect was tentatively ascribed to inability to utilize glycogen and it is suggested in an addendum that this is due to the

absence of phosphorylase a and b in muscle. This defect was manifested clinically by a limited exercise tolerance. The duration of work was greatly improved by infusion of glucose or fructose. Fructose was effective at a much lower plasma concentration than glucose. It is therefore concluded that fructose can traverse the muscle cell membrane and contribute significantly toward the fuel for muscular work in this particular patient G.J.H.

Pomeranze, Julius; Stone, Martin L.; and King, Edward J. (Dept. Obst. & Gynec., Dept. of Med., New York Medical College, Metropolitan Med. Center, New York, N.Y.): THE OBSTETRIC IMPORTANCE OF OBESITY AND "BENIGN" GLYCOSURIA IN PREDIAGNOSIS DIABETES. Obst. & Gynec. *13*: 181-84, February 1959.

The histories of 643 diabetic women are reviewed. A family history of diabetes was found in 62 per cent, of obesity in 88 per cent, of benign glycosuria in 15 per cent and abnormal obstetrical history in 19 per cent. The prediabetic state or its pathological counterparts exist years before carbohydrate abnormalities are apparent. C.A.V.

Radding, Robert S. (Houston, Tex.): NEW ORAL HYPOGLYCEMIC DRUGS IN DIABETES: CLINICAL EXPERIENCES. Texas J. Med. 55:110-14, February 1959.

Six patients were selected for trial with chlorpropamide and in all patients it was found to be an effective hypoglycemic agent. In an addendum the author states that it was discontinued in two patients because of the occurrence of dermatitis. Seven patients were chosen for a trial with phenethyldiguanide, all of whom were severe and unstable diabetics. It was found to be an effective agent for supplementing the effect of insulin but the need for close surveillance of the patients is stressed. B.F.K.

Ricketts, Henry T. (Dept. of Med., Billings Hosp., Chicago, Ill.): DOES RIGID CONTROL OF THE BLOOD SUGAR PREVENT THE CARDIOVASCULAR COMPLICATIONS OF DIABETES? Illinois M. J. *115*:267-68, May 1959.

Possible factors involved in the production of vascular lesions in patients with diabetes mellitus are discussed. These factors include biochemical abnormalities and inherited traits. Neither plays a preponderant role though a biochemical abnormality acting on genetically susceptible blood vessels may be a suitable explanation. Data from the Joslin clinic show little retinal and renal disease in well controlled patients and considerably more in poorly controlled ones. The effect of good control of diabetes on atherosclerosis is less well delineated. At present, it is prudent to control diabetes as well as possible. R.L.J.

Sargent, F., II; Johnson, R. E.; Robbins, E.; and Sawyer, L. (Dept. of Physiol., University of Illinois, Urbana, Ill.): THE EFFECTS OF ENVIRONMENT AND OTHER FACTORS ON NUTRITIONAL KETOSIS. Quart. J. Exper. Physiol. *43*:345-51, October 1958.

During studies of survival rations for air crews, nutritional observations were made on 198 healthy young men continuously for six weeks. In forty-eight of these subjects nutritional ketosis was produced by two weeks of complete starvation; by a diet high in fat but low in protein and carbohydrates; or by a diet high in fat and protein but devoid of carbohydrate. Paired feeding technics were used for groups of two to four subjects. By factorial analysis the relation was determined between nutritional ketosis and five variables: (1) environmental temperature (winter and summer); (2) total caloric intake (0, 1,000 and 2,000 cal./day); (3) water balance (unlimited water and water restricted to 910 ml./day); (4) duration of regimen (one and two weeks); and (5) work load (a daily march of five and twenty kilometers). As judged by ketonuria and ketonemia, the ketogenicity of any diet (including starvation) was reduced significantly by increase in environmental temperature, by increase of caloric intake with the same diet, and by a reduction of fluid intake. Ketosis diminished in the second week of any regimen, and tended to be less with increased daily work. These results may modify orthodox concepts of nutritional ketosis based on the "ketogenic/antiketogenic ratio" of Shaffer. G.A.W.

Thompson, Marilyn M.; and Mayer, Jean (Dept. of Nutrition, Harvard School of Public Health, Boston, Mass.): HYPOGLYCEMIC EFFECTS OF SACCHARIN IN EXPERIMENTAL ANIMALS. Am. J. Clin. Nutrition 7:80-85, January-February 1959.

Saccharin (o-sulfobenzoic acid imide) was administered in varying amounts to obese-hyperglycemic mice, control mice and normal rats in acute and chronic experiments. Both rats and mice exhibited hypoglycemia after acute injection of saccharin if they had been fed during the study, and fasting prevented this response. Obese-hyperglycemic mice exhibited hypoglycemia from administration of 125 to 175 mg. saccharin daily over four weeks. The mechanism of this action is unknown, but it is probably not similar to that of the sulfonylureas. A.R.C., JR.

Vander, John B. (Pondville Hosp., Walpole, Mass.): THE ASSOCIATION OF DIABETES MELLITUS AND CARCINOMA OF THE ENDOMETRIUM. Am. J. Obst. & Gynec. 77:243-45, February 1959.

The author, interested in the report that diabetes mellitus occurred more frequently in patients with carcinoma of the cervix, reviewed the cases of 483 patients and found an incidence of diabetes of 5.6 per cent as opposed to 5.4 per cent in the general population of the same sex and age. He feels that his study does not support any relationship between the two diseases. R.L.J.

Waddell, William R.; Geyer, Robert P.; Hurley, Nancy; and Stare, Fredrick J. (Dept. of Nutrition, Harvard Sch. of Public Health, Dept. of Surg., Harvard Med. Sch., Massachusetts Gen. Hosp., Boston, Mass.): ABNORMAL CARBOHYDRATE METABOLISM IN PATIENTS WITH HYPERCHOLESTEROLEMIA AND HYPERLIPEMIA. Metabolism 7:707-16, November 1958.

Twenty patients with idiopathic hypercholesterolemia are reported in this study. Insulin tolerance tests showed abnormal sensitivity to insulin in sixteen of seventeen tested and glucose tolerance tests were abnormal in eighteen of twenty. A reduction in serum cholesterol concentration followed intravenous infusion of glucose in both hypercholesterolemic and normal subjects. Glucagon caused normal increase in blood glucose concentration. The author suggests that relative pancreatic insufficiency leads to a "diabetes-like" state which in turn leads to an elevated serum cholesterol. There were fourteen males in the hypercholesterolemia group and eight gave a history of heavy consumption of alcohol for a period of years followed by almost complete abstinence prior to the first sign or symptoms of vascular disease. This suggests hepatic impairment. However, none of the women used significant quantities of alcohol. R.W.S.

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Nineteenth Annual Meeting

The Nineteenth Annual Meeting of the American Diabetes Association was held in Atlantic City June 6-7, 1959. Names of Officers and Councilors elected for the 1959-60 organizational year are listed on the above masthead.

SCIENTIFIC SESSIONS

Twenty-four papers, a panel discussion on oral hypoglycemic agents, and the Banting Memorial Lecture were presented durthe Scientific Sessions. Sixteen papers were listed by title, author and abstract in the printed program.

Under the Chairmanship of Franklin B. Peck, Sr., M.D., the Committee on Scientific Programs included the following members: Harvey C. Knowles, Jr., M.D., Vice Chairman; Francis D. W. Lukens, M.D., Vice Chairman; Thaddeus S. Danowski, M.D.; Laurance W. Kinsell, M.D.; Henry E. Marks, M.D.; William C. Stadie, M.D.; Laurentius O. Underdahl, M.D.; and Robert H. Williams, M.D.

The Banting Memorial Lecture was delivered by George W. Thorn, M.D., Hersey Professor of the Theory and Practice of Physic, Harvard Medical School, Physician-in-Chief, Peter Bent Brigham Hospital, Boston. Titled "The Adrenal and Diabetes: Some Interactions and Interrelations," it is published as the first article in the current issue of DIABETES.

On invitation, Marvin D. Siperstein, M.D., Ph.D., recipient of the 1959 Lilly Award, presented a paper entitled "Studies on the Lipogenic Defect in Diabetes."

ANNUAL BANQUET

The Banquet, held in the Vernon Room of Chalfonte-Haddon Hall on Saturday evening, June 6, at 7:30 p.m., was attended by 367 guests, more than have assembled for any other banquet in ADA history. Invocation was offered by Deaconess Maude Behrman, Atlantic City. The annual Address of the President was delivered by Alexander Marble, M.D.

WHICH WAY SHALL WE GO?

ALEXANDER MARBLE, M.D., BOSTON

Since the President is allowed a free hand in selecting a subject for the address given at the Banquet, there are various noncontroversial topics which I could have chosen. It would have been easier, and perhaps wiser, to have done this. However, since the American Diabetes Association at the present time finds itself in the process of deciding as to the type of organization it wishes to be, I feel obliged to discuss this

matter with you briefly this evening. Although it is well known to members of the Council and to the members of various committees, it deserves presentation to a larger group.

This is the Nineteenth Annual Meeting of the American Diabetes Association. The first such meeting was held in Cleveland on June 1, 1941, on a Sunday preceding the opening of the meeting of the American Medical Association. A year before, on June 12, 1940, a committee for the establishment of an American Diabetes Association had met in New York City. Twenty-six physicians were present and adopted a constitution and bylaws. In this June 1940 meeting as well as in an earlier one in April 1940, representatives of existing local diabetes organizations took an active part. Such local groups were then to be found in New York, Philadelphia, Detroit, Cincinnati and Rochester, New York. In this connection, it is noteworthy that in his address as the Association's first president, Dr. Cecil Striker stated that "it should be one of the purposes of the American Diabetes Association to encourage the formation and integrate the activities of the various local diabetes organizations." The second president, Dr. Herman O. Mosenthal, appointed a "Committee on Foundation of Local Societies."

As one reads the early records of the American Diabetes Association, one gains the impression that in the minds of its founders, this was to be a professional society of physicians with associate membership for dietitians and other ancillary workers; that the Association through its national office should attempt to encourage the activities of local groups with contact through the physicians heading up such local societies; and that if lay components of local groups existed or were organized, they should be the direct responsibility of the local professional group concerned. The original thought was to have professional guidance at both the national and local level. This continues to be a basic principle of our organization.

As the years have gone by, the activities of the Association have increased steadily. Shortly after the end of World War II, a definite national headquarters office, apart from any physician's office, was set up with a full-time Executive Secretary in charge. The office staff has grown to include some twenty hard-working people who are loyal to the Association and devoted to their jobs. In the field of *professional education,* a scientific meeting and a postgraduate course, both of high quality, are held annually. The Association's bimonthly journal, DIABETES, has achieved a place among the good medical publications of the country. Through a speakers' bureau, funds are available to Affiliates to help defray the expenses of guest lecturers. In the area of *patient education,* the bimonthly magazine, ADA FORECAST, fills a real need; its circulation now is well over 50,000. *Public education* is furthered by means of the annual Diabetes Detection Drive and the information distributed at that time by means of newspapers, magazines, radio, television, leaflets, etc. The Association has taken pride in maintaining these educational activities as a public service with no tie-in to the raising of money. Because of this policy it has gained in favor and in stature among other national organizations. In *research* the Association has a deep and continuing interest; many of its leading members devote their lives, in whole or in part, to activities designed to further knowledge regarding the nature and treatment of diabetes. In a very modest way the Association supports research directly by the awarding of fellowships to promising young investigators.

ALEXANDER MARBLE, M.D., PRESIDENT, 1958-59

These activities cost money and so over the years there have been countless discussions as to the best means of obtaining such. During the early formative years, as now, a sizable portion of the total expenses was defrayed by yearly grants from large companies, chiefly manufacturers of pharmaceuticals. Without these contributions, the work of the Association would not have been possible and we cannot adequately express our debt and gratitude to the donors. Although all have recognized that this source of funds is uncertain and that ways and means should be sought to find other support for our expanding activities, the Council has steadfastly reaffirmed its conviction that money should be raised by dignified methods, chiefly from diabetic patients, their families and friends. Despite earlier fears, the financial status of the Association has improved in recent years. This has been due to the fact that certain activities pay for themselves, presenting no burden, and to the increasing amount of money received from Corporate Members, Foundations, private donors, readers of FORECAST and contributions from Affiliate Associations.

However, a problem has arisen at the local level. Certain Affiliates felt the need for more money for local expenditure and asked for less rigid rules regarding fund raising. In an attempt to answer this plea, the Council in 1956 agreed to modify the stand of the Association by allowing general public fund raising at the local level by such Affiliates as desired to undertake this, provided such activities were carried on in a dignified manner, were divorced from diabetes detection and other public service activities, did not use mass media and did not utilize fear technics.

Since 1956 certain developments have taken place, among

which are the following: (1) Various Affiliates have become allied with their local United Fund or Community Chest organizations. This plan has worked well and has provided funds adequate for the support of a local office, executive director and secretary, and has allowed for such activities as meetings, diabetes detection, etc. (2) Certain Affiliates have become restive and have carried out programs of public fund raising with features considered undesirable even if viewed by the liberalized standards set up by the Council of the American Diabetes Association. These local Affiliates have desired to raise large sums of money with the conviction that such was needed for research.

It is obvious, then, that there are differences of opinion as to the type of organization which the American Diabetes Association should become. Of the various possibilities, other than the maintenance of the present type of structure and principles, certain may be singled out:

(1) We can contract our structure, become more nearly a strictly professional organization of physicians, and can disavow any responsibility for lay components of Affiliate societies. Although I have heard a few of our members speak in favor of this plan of action, I doubt that any considerable number would want to step out of the field of public service in this way.

(2) We could forget our misgivings in the past and become a national voluntary health agency with a large program of public fund raising. This would mean a tremendous expansion of our activities, a great enlargement of our central office, and quite a radical change in the composition of our organization. It would seem only reasonable that if the public at large works for and donates large sums of money to a national organization, it deserves a part in its administration and operation and a definite voice in the making of its policies. The change in organization would mean that voluntary workers would be recruited to solicit funds from door to door, that appeals for money for diabetes would appear in newspapers and on billboards everywhere and that radio and television time would be secured. I have no way of knowing how many of our more than 2,500 members would like the American Diabetes Association to be this kind of organization. From private conversation, I know of many who would not and I know that there are many wives of members who shudder at the thought of having to take part in still another house-to-house campaign for money. Furthermore, one senses in the general public a growing disapproval of multiple campaigns of fund raising by health organizations.

(3) A third suggestion has been to continue along the present lines but making even looser and less rigid, if such be possible, the relationship of Affiliates to the national organization. In general, the Affiliate would be allowed to go its way alone and to engage in any and all activities considered reasonable by its own Board of Directors. Some favor this plan strongly but many of our members deplore it as leading only to insecurity and disorganization rather than organization.

These, then, are the problems which we face. Which way shall we go? Shall we contract to a strictly professional society with fewer public service activities, shall we expand to a voluntary health agency with a large-scale program of public fund raising, shall we make the relationship with Affiliates even looser and allow any locally-approved type of activity, or shall we continue our present policy in which limited programs of fund raising by dignified methods are allowed at the local level? You will be interested to know that at its meeting yesterday the Council voted to follow at present the last-named course, difficult though that may be.

This does not imply that there is a belief that our present organizational structure is perfect. Far from it! It is woefully inadequate in many respects. Above all, there is need for clear definition of the relationship of Affiliate societies to the national organization and the establishment of a truly usable structure. I assure you that the Council has these matters very much on its mind and has established working groups who are considering these problems. By continuing and intensive work I am confident that proper answers can and will be worked out. I plead for patience on the part of all concerned. Meanwhile, I urge that all Affiliates and all members do their best to abide by the principles of the Association as presently set up.

In the nineteen years since its organization, the American Diabetes Association has achieved an enviable and somewhat unique position among medical societies in this country. Its achievements form an excellent record of which we may well be proud.

Let us all act wisely so that we may preserve what is good in our present situation and constantly improve our activities to the end that the welfare and the outlook for the future of persons with diabetes may be advanced.

THE LILLY AWARD

Immediately following the Address of the President, the 1959 Lilly Award consisting of $1,000 and a medal, was presented to Marvin D. Siperstein, M.D., Ph.D., for his work on fat metabolism. The Award, the third given annually by Eli Lilly and Company, is made to recognize demonstrated research "in the field of diabetes, taking into consideration independence of thought and originality." Dr. Siperstein's work has provided an understanding of the relationship between carbohydrate and fat metabolism, and an explanation for the defect in fatty acid synthesis in diabetes. Now thirty-three years of age, Dr. Siperstein is Associate Professor of Internal Medicine, University of Texas Southwestern Medical School, Dallas. He received three degrees from the University of Minnesota, including one in Medicine, and also holds a Doctorate in Physiology from the University of California.

At Nineteenth Annual Meeting: Banting Medals were awarded to GEORGE W. THORN, M.D. (left); to ALEXANDER MARBLE, M.D. (standing at the right of HENRY T. RICKETTS, M.D., a past President); and to E. T. BELL, M.D. (right).

THE BANTING MEDAL

After the presentation of the Lilly Award, the Banting Medal was given to George W. Thorn, M.D., the Banting Memorial Lecturer, by Alexander Marble, M.D., President. Banting Medals also were presented to E. T. Bell, M.D., Emeritus Professor of Pathology, University of Minnesota Medical School, Minneapolis, and to Dr. Marble, retiring President. The presentation to Dr. Marble was made by Henry T. Ricketts, M.D., of Chicago, a past President of the ADA.

The Banting Medal is presented at the Annual Meetings of the Association to its retiring President, and to its Banting Memorial Lecturers. It is also awarded on occasion to others "for distinguished service in the interest of doctor and patient." It has become the honored symbol of the American Diabetes Association, and an award much treasured by its recipients. A complete account of its history will be found on pages 332-33 of the July-August 1955 issue of the Journal.

BANQUET HIGHLIGHTS

A highlight of the Banquet was the tribute paid by the Association to Elliott P. Joslin, M.D., Honorary President of the ADA, on this, the date of his ninetieth birthday. A handsome Citation signed by each member of the Council was given him for "his distinguished contributions to the medical profession through his work as investigator, practitioner, and educator in the field of diabetes." Dr. Charles H. Best, co-discoverer of insulin, made a special trip from his home in Toronto to present the Citation.

Guest speaker of the evening was Boland Hughes, M.D., Professor of Clinical Urology, University of Pennsylvania School of Medicine, Philadelphia, who talked on "The Contemporary Scene in the U.S.S.R."

Miss Anna Smrha, of Lincoln, Nebraska, was awarded the annual "Citation as an Outstanding Layman" in recognition "of the ability and fine spirit with which she has dedicated herself to the activities of the Nebraska Diabetes Association for the benefit of diabetics in Nebraska and for her devotion to diabetic children in the direction of Camp Floyd Rogers." The presentation was made by Henry E. Oppenheimer, M.D., Chairman of the Assembly of Delegates.

CHARLES H. BEST, M.D. (left), co-discoverer of insulin, presents Citation to ELLIOTT P. JOSLIN, M.D., on his ninetieth birthday.

ANNUAL BUSINESS MEETING

The Annual Business Meeting of the American Diabetes Association was held June 7. The remarks by Alexander Marble, M.D., President, were followed by: reports of the Secretary, Treasurer, Executive Director and the Nominating Committee; and the Installation of the Incoming President.

Remarks by the President

I am happy to observe that we have far more than a quorum present for our Annual Business Meeting. I am grateful for the excellent attendance.

The first item on the program is that of remarks by the President. As my predecessors have usually stated, by this time everyone is tired of hearing the President speak and almost nothing more is needed or wanted from him. However, I would be remiss if I did not express my sincere thanks to all those members who have labored so long and so hard during the past year. Mr. Connelly has told us that there are some fifty separate events scheduled during this week including committee meetings, Council meetings, scientific sessions, banquet, etc. Some of the committees are large and some are small but all involve hours and days of work, voluntarily performed, by the members of this society. It is heartening for the President to have the support of fellow members who work and give freely of their time year after year. As anyone who has been in the Council or Executive Committee knows, there is a constant effort made to try to draw into this working group still others, particularly young members, who will give time, thought and effort to the Association. If you know any young men or women, who are able, willing and dependable, I am sure that Dr. Lukens would like to know about them for the coming year.

I also want to pay tribute again, as I have in the past, to Mr. Connelly and Mr. Bernat and the others in the wonderful staff at the national office in New York. They are hard-working and devoted. I have never before seen such evidence of loyalty to an organization as they exhibit.

Finally, I wish to thank the members of the Association for the privilege and honor of having served during this past year as your President.

ALEXANDER MARBLE, M.D.

Report of the Secretary

Mr. President, and members of the Association. As your Secretary, I am very pleased to report that the Association is doing excellent work.

The Twentieth Annual Meeting will be held in Miami Beach on June 11-12, 1960, at the Hotel Deauville.

Our Postgraduate Course Series has been well received, and the program for the next Course, the Eighth, appears to be outstanding. The Course will be held Jan. 20-22, 1960, at the Ambassador Hotel in Los Angeles.

The total membership of our Association is now 2,532 with twenty applications pending.

Our Research Fellowship program is progressing, and it is a pleasure to report that we recently received a sizable bequest which will enhance continuation of this program. For the 1959-60 academic year, the following Fellowships have been awarded:

Bruce M. Carruthers, M.D., Department of Medicine, Hospital of the University of Pennsylvania, to work with Francis C. Wood, M.D.

Jurgen Steinke, M.D., Baker Clinic Research Laboratory, Department of Medicine, Harvard University Medical School, Boston, to work with George W. Thorn, M.D., and Albert E. Renold, M.D.

June W. Pryor, M.D., Baker Clinic Research Laboratory, Peter Bent Brigham Hospital, Boston, to work with George W. Thorn, M.D., and Albert E. Renold, M.D. (*Editor's Note: Dr. Pryor subsequently transferred to the University de Louvain where she will work with Drs. C. de Duve and Jacques Berthet.*)

Further, Dr. David Norman will continue his work during the second year of the three-year Adler Foundation Research Fellowship at the California Institute of Technology.

The Committee on Scientific Awards has selected Basil N. Spirtos, of the University of Iowa, as the winner of the $250 award provided by the St. Louis Diabetes Association for the best paper in the 1958-59 Medical Student-Intern Essay Contest reporting original work. The title of his paper is "The Effect of Hypothalamic Lesions on Insulin Sensitivity." Honorable mention is being given to Stewart B. Dunsker, of the University of Cincinnati, for his paper entitled "A Review of the Chemical Nature of Insulin and Studies in the Preparation of a Mercury Derivative of Partially Reduced Insulin."

The $100 prize for the best review article or case report has been awarded to Thomas N. Vincent, of the University of Colorado, for his paper entitled "On the Mechanisms of Monosaccharide Absorption in the Small Intestine: A Review." Honorable mention in this prize category is being given to C. R. Joseph Caskin, Jr., of Emory University, for his paper entitled "Studies on Potassium in Diabetic Acidosis: A Review."

Time does not permit a report of the activities of all of the various committees and boards dealing with the aims and objectives of our organization, as there are thirty-eight, with more than 400 members. To cite two: The Subcommittee on Teaching of Diabetes in American Medical Schools is doing an exceptional job; the Committee on Employment continues its good work and is highly regarded by industry and other agencies.

ADA FORECAST continues to be a most unique service in the field of patient education, and its subscribers now number approximately 55,000, including the Canadian Edition. The Journal DIABETES is showing great strides under the capable editorship of Doctors William C. Stadie and Irving Graef.

On behalf of the membership, I wish to express our appreciation to Mr. Connelly and his excellent staff for very efficient management and guidance in our work.

E. PAUL SHERIDAN, M.D.

Report of the Treasurer

It is my pleasure to report that the American Diabetes Association completed the fiscal year ending March 31, 1959, with an excess of income over operating expenses of $25,000. An additional $8,000 was spent on special appropriations, giving a net figure of $17,000.

Our total income for the year amounted to $389,000 and our program cost us $364,000 plus the aforementioned $8,000 for appropriations.

A comparison of the cost of our present program with the programs of five and ten years ago demonstrates substantial

expansion of the Association's activities. Ten years ago our expenses were $58,000, five years ago $175,000 and the past year, as reported, $372,000. Expenses have increased to over six (6) times those of ten (10) years ago and more than double those of five (5) years ago. It is interesting to note that expenses, which we may consider as representing program expansion and continuing progress, have increased on *an average* of about $32,000 a year for the past ten years. We have been able, each year, to secure additional funds required to support our increased activities.

As of March 31, 1959, our total assets amounted to well over one-half million dollars.

Income from contributions during the fiscal year 1958-59 is almost $170,000 or 43 per cent of our total income. Of this amount, $157,000 was deposited to the General Fund and $13,000 to the Research and Fellowships Fund. The balance of $219,000 or 57 per cent represents income earned from membership dues, DIABETES Journal subscriptions, ADA FORECAST subscriptions, sale of testing materials, printed materials and pamphlets, interest on savings accounts and the Seventh Postgraduate Course.

It gives me great pleasure at this time to acknowledge certain contributions. From Affiliate Associations a total of $6,239.70, from Corporations $123,885 and from Foundations, $15,363. Of the larger contributions, I would like to acknowledge the following:

From Corporations

Ames Company	$20,000.00
Atlas Powder Company (for research)	6,000.00
Becton, Dickinson and Company	1,500.00
Chas. Pfizer and Company, Incorporated	1,000.00
Eli Lilly and Company	50,000.00
E. R. Squibb and Sons	10,000.00
The Upjohn Company	35,000.00

From Foundations

Adler Foundation (for research)	$ 5,000.00
Rockefeller Brothers Foundation	2,500.00

While the total amount from Foundations is not great, it is encouraging to know that a total of forty-three (43) Foundations made gifts or grants to us last year—twenty (20) of them for the first time.

The expense of activities for the fiscal year ending March 31, 1959, totaled $372,000 and was spent as follows:

On Professional Education	$113,500
On Patient Education	121,000
On Public Education and Case Finding	77,300
On Research and Fellowships	22,900
On General Administration and Appropriations	37,300

I believe that we all may be gratified with the results of our operation during the past fiscal year. In the face of increased expenses due to a steadily expanding program, we have found the means to secure the financial support required to carry out these activities.

As each year our expanding program requires more money, we hope that we may look forward to increased financial support from contributors and income producing activities.

THOMAS P. SHARKEY, M.D.

Report of the Executive Director

Dr. Marble, Officers and Members of the American Diabetes Association: Considerations of time, which always presses heavily upon us at our Annual Meeting, require those reporting to you to telescope some of the more significant activities of the American Diabetes Association.

As indicated by Doctors Sharkey and Sheridan, all in all this past year has been one of heavy growth. Our financial contributions demonstrated the continuing faith and support of the Association's members and friends. The budget for 1958-59 was the largest to date and the 1959-60 budget represents a 13 per cent increase over the previous fiscal years.

As you have heard from the Secretary's report, the Association in 1958-59 achieved a new membership high. It now has over 2,500 members. Completing the picture of healthy growth has been the greater organizational activity—mainly by the various national committees—which was extended throughout the past year.

A significant project which may be of interest to you is a new publication entitled A COOKBOOK FOR DIABETICS, to which Dr. Marble referred in the President's Address last evening. The book will be available at a dollar a copy so as to enable virtually every diabetic to secure one. This 176-page book contains the best of Deaconess Maude Behrman's recipes and menus which have appeared over the past twelve years in the ADA FORECAST. Several thousand orders have already been received as a result of the initial announcement.

The communication media of the nation accorded the 1958 Diabetes Week the greatest attention it has ever received in the history of that annual observance. Certainly the major articles in *Reader's Digest*, the *Saturday Evening Post* and *McCall's*, reaching 65,000,000 persons, represented outstanding recognition of the efforts of the American Diabetes Association and its Affiliates. It will be difficult to surpass, or even equal, this showing in the years ahead.

I would be less than frank, however, if I did not also report to you that the year just past was not without its problems. These problems were, for the most part, organizational in nature. Several projects which we had hoped to achieve had to be held in abeyance because of more pressing demands upon the time and energies of the national office. Such projects are, of course, receiving top priority in 1959.

On the whole, the organization recorded a most satisfactory year. For me, *personally*, it rounds out a decade of affiliation with the American Diabetes Association—a decade which indeed has proved very rewarding to me. It is a real privilege to work with this Association.

As I mention each year, the American Diabetes Association is an organization of individual members and all of them have the same rights and privileges. This is the principle that guides the national office. For those of you who can visit the national office, the staff and I extend a most cordial welcome.

For those of you who do not expect to be in New York during the coming year, I will be delighted to meet and talk with you at the registration desk this afternoon.

This report would be totally incomplete if I did not express my great appreciation to the President, to all the Officers and Councilors, Committee Chairmen and Committee members, and Editors of our publications and indeed to the entire membership, for their support and cooperation.

J. RICHARD CONNELLY

Resolution by George F. Schmitt, M.D.

The following resolution was offered by Dr. Schmitt, Miami, Florida:

"Whereas, the preparation of the Scientific Exhibits of the American Diabetes Association is difficult and an onerous task, and

"Whereas, the preparation of the Scientific Exhibits is essentially the work of the Chairman;

"Therefore be it resolved: that the American Diabetes Association in convention assembled express its approbation and appreciation to its Chairman, Dr. Marshall I. Hewitt of New York."

(*The resolution was seconded from the floor and was adopted by acclaim.*)

Report of the Nominating Committee

The Nominating Committee is pleased to report the following slate:

For President, Dr. Francis D. W. Lukens, of Philadelphia; for First Vice President, Dr. Franklin B. Peck, Sr., of Indianapolis; for Second Vice President, Dr. Blair Holcomb, of Portland, Oregon; for Secretary, Dr. E. Paul Sheridan, of Denver; for Treasurer, Dr. Thomas P. Sharkey, of Dayton.

For Councilors for term ending in 1962: Dr. Louis K. Alpert, of Washington, D.C.; Dr. Jerome W. Conn, of Ann Arbor; Dr. Edwin W. Gates, of Niagara Falls; Dr. Harvey C. Knowles, Jr., of Cincinnati; Dr. Arnold Lazarow, of Minneapolis; and Dr. Laurentius O. Underdahl, of Rochester, Minnesota.

(*It was moved, seconded and voted that the nominations be closed. All nominees were duly elected.*)

HENRY T. RICKETTS, M.D., *Chairman*

Installation of Incoming President

ALEXANDER MARBLE, M.D., *retiring President*: I will now ask the new President of the organization, Dr. Francis D. W. Lukens, to come forward. Luke, it is a great pleasure to welcome you here. I know that the Association will be in excellent hands during the coming organizational year and as a token of the responsibility which I now turn over to you, I hand you this official gavel of the Association. Good luck!

Remarks of Newly-Installed President

Thank you, Alex, and thank you all, my friends, for trusting me, goodness knows why.

If I could do it, I would recall the remarks made last night by Dr. Ricketts about Dr. Marble's splendid term of office as President. He has proved an executive of unusual ability and he has set me an example which I cannot follow but I can at least keep in mind.

In undertaking this office, I have these thoughts: One man can't do much but he has the pleasure of working with several colleagues. The first of these is the Council. This is a remarkable collection of men. I have heard them disagree and fight and go on but they all have enough character and enough underlying purpose to pull together as well as possible for the objectives of this Association.

There is, of course, our office in New York, the really round-the-clock group of workers, on whom we all lean so heavily since the society has grown so much larger.

And finally, there is the entire membership. I speak for the Council as well as I am able when I say that I take this office and we all take our offices for one primary purpose, that is to serve all of the membership in the accomplishment of the purposes of our Association.

I think that it is now time to declare this meeting adjourned with no further formalities and from here on I hope to hear from all of you unofficially as much as possible. The meeting is adjourned. FRANCIS D. W. LUKENS, M.D.

LOS ANGELES— 8TH POSTGRADUATE COURSE

Los Angeles plays host early in 1960 to the American Diabetes Association, whose Eighth Postgraduate Course in Diabetes and Basic Metabolic Problems will be given at the Hotel Ambassador on Jan. 20, 21 and 22. The Course Director is Thaddeus S. Danowski, M.D., Chairman of the ADA Committee on Professional Education, and Roy F. Perkins, M.D., the Association's Governor for Southern California, is Chairman of the Local Committee. The Course will be given in cooperation with the Schools of Medicine of the College of Medical Evangelists, University of California at Los Angeles and the University of Southern California.

The tentative program, in addition to patient demonstrations, will include these topics:

FUNDAMENTALS OF DIABETES: Interrelations of Intermediary Metabolism; Endocrine Aspects of Intermediary Metabolism in the Normal; Pathologic Anatomy of Diabetes; Disturbances of Normal Physiology in the Diabetic State; Actions of the Hypoglycemic Agents (Insulin and Oral Compounds); Panel Review on Therapeutic Implications and Fundamentals of Diabetes and of Oral Hypoglycemic Agents.

DIAGNOSTIC AND THERAPEUTIC CONSIDERATIONS: The Potential Diabetic; The Juvenile or Unstable Diabetic; The Maturity-onset (Stable) Diabetic; The Diabetic under Stress; Round-table Conferences.

CLINICAL SESSIONS IN DIABETES, or DIABETES IN REVIEW: Skin Manifestations of Diabetes; Unusual Biochemical Manifestations of Diabetic Acidosis; Secondary Diabetes; Renal Problems (Pyelonephritis, Kimmelstiel-Wilson Disease); Neurological Changes in Diabetes (Peripheral Neuritis, Neurogenic Bladder, Visceral Neuropathy, Neuropathic Joints); Eye Changes in Diabetes (Cataracts, Retinitis); Hypoglycemia (to Insulin and Oral Agents); Round-table Conferences.

VASCULAR COMPLICATIONS OF DIABETES: Vascular Changes as Observed by Electron Microscopy; Dietary Factors in Vascular Disease; Coronary Artery Heart Disease in the Diabetic; Peripheral Vascular Surgery in the Diabetic; Vascular Changes in Diabetics of Twenty or More Years' Duration; Panel Review on Vascular Problems in Diabetes.

DIABETES ON THE RESEARCH FRONTIER: Relative Importance of the Liver and Extrahepatic Tissues in the Metabolism of Glucose; Liver—Cross-Circulation Studies; Intermediary Metabolism of Extrahepatic Tissues; Special Phases of Insulin Action (Insulin Antibodies, Insulin Antagonists); Newer Diagnostic Methods in Diabetes.

Registration fees are $40 for Association members and $75 for nonmembers. All inquiries pertaining to the Course should be directed to the national office of the Association, 1 East 45th St., New York 17, N.Y.

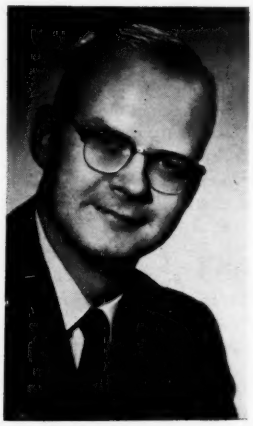
WINNERS OF 1958-59 MEDICAL STUDENT-INTERN ESSAY CONTEST

Basil N. Spirtos, M.D., Iowa City, and Thomas N. Vincent, M.D., Denver, have been selected by the Committee on Scientific Awards of the American Diabetes Association as the winners of the 1958-59 (seventh) Medical Student-Intern Essay Contest.

An award of $250, made possible by the St. Louis Diabetes Association, has been presented to Dr. Spirtos for the best paper submitted in the field of diabetes reporting original work, whether laboratory investigation or clinical observation. Dr. Vincent was awarded $100 for the best paper in the category of review article or case report.

Stewart B. Dunsker, Cincinnati, and C. R. Joseph Caskin, Jr., Atlanta, received honorable mention in the best paper reporting original work and in the best case report or review article categories, respectively. Both men received a one-year subscription to DIABETES.

BASIL N. SPIRTOS, M.D.



THOMAS N. VINCENT, M.D.

The prize-winning paper by Dr. Spirtos is entitled "The Effect of Hypothalamic Lesions on Insulin Sensitivity." Dr. Spirtos was born in 1929 in Campbell, Ohio, and graduated from Ohio State University in 1950. At the State University of Iowa he obtained his M.S. in 1953 and his Ph.D. in 1955. He received his M.D. in 1959 from The College of Medicine, State University of Iowa. He is at present serving his internship at the Los Angeles County General Hospital. Dr. Spirtos is a member of the Society of the Sigma Xi, the American Association of Anatomists, The Endocrine Society and The Society for Experimental Biology and Medicine. He has been the recipient of the following awards: Book review award presented by the Department of Public Health and Preventive Medicine of the State University of Iowa for the academic year 1956-57; Fisher Foundation Scholarship 1958; Student speaker during the freshman medical student orientation program (Sept. 24, 1958) and during the Annual Iowa State Pre-Medical Conference (Nov. 7, 1958); Borden Undergraduate Research Award in Medicine (June 11, 1959). He has also published numerous papers in several medical journals. His interests for the future lie in teaching and research in basic and clinical endocrinology.

"On the Mechanisms of Monosaccharide Absorption in the Small Intestine: A Review" is the title of Dr. Vincent's paper. Born in 1931 in Salt Lake City, he attended public school in Denver and then Princeton University where he obtained his B.A. degree in 1952. He worked as a research chemist in Cincinnati until 1954, at which time he enlisted in the Army and was stationed at Walter Reed Army Hospital, Washington, doing biochemistry research until 1955. Upon separation from the Service he attended the University of Colorado School of Medicine where he received his M.D. in 1959. At the present time he is interning at Walter Reed Army Hospital.

Mr. Dunsker, whose paper, "A Review of the Chemical Nature of Insulin and Studies on the Preparation of a Mercury Derivative of Partially Reduced Insulin," won honorable mention, was born in Cincinnati in 1934. He completed his public school education in Cincinnati, graduating as president of his senior class in 1952. He graduated from Harvard University, cum laude, in 1956, and entered the College of Medicine, University of Cincinnati, with the class of 1960. At the present time he is a senior and a member of Pi Kappa Epsilon honorary medical fraternity. In the past five years Mr. Dunsker's research projects have involved the chemistry of insulin, phosphate transport in erythrocytes, and phosphate metabolism in metabolic acidosis. He is currently working in the Department of Hematology, investigating carbohydrate metabolism in leukocytes.

Mr. Caskin, whose paper entitled "Studies on Potassium in Diabetic Acidosis: A Review" also received honorable mention, was born in Macon, Georgia, in 1935. He obtained his A.B. degree from Emory University in 1957, and is at present a junior at Emory University School of Medicine. He belongs to Phi Chi Medical Fraternity. Married, he now resides in Atlanta. He intends to specialize in internal medicine.

EIGHTH GRADUATE AND MEDICAL STUDENT-INTERN ESSAY CONTEST

The Council of the American Diabetes Association has accepted the recommendation of the Committee on Scientific Awards to change the name of the yearly Essay Contest to the "Graduate and Medical Student-Intern Essay Contest" beginning with the present 1959-60 season. The 1959-60 Contest will now be open to graduate students, medical students, interns and physicians within two years after their graduation from medical school. With this change graduate students are eligible to participate in the contest.

An award of $250 will be given to the author or authors of the best paper reporting original work, whether laboratory investigation or clinical observation. One hundred dollars ($100) will be awarded for the best review article or case report.

The papers will be judged on the basis of the value of the material and the method of presentation. Any subject relating to diabetes and basic metabolic problems may be selected.

Members of the American Diabetes Association and subscribers to DIABETES are asked to encourage graduate students, medical students, interns and physicians within two years after their graduation from medical school to enter the contest.

Contestants should submit the original and two copies of their papers. Typewritten and double-spaced, all manuscripts should be mailed by April 1, 1960, to: Committee on Scientific Awards, American Diabetes Association, Inc., 1 East 45th St., New York 17, N.Y.

THE LILLY AWARD

Jan. 1, 1960, is the deadline for receipt of nominations for the fourth Lilly Award, which will be given at the Twentieth Annual Meeting, June 11-12, in Miami Beach, Florida. The following stipulations govern the contest for this annual award, which is supported by Eli Lilly and Company and consists of $1,000 and a medal.

Purpose: To recognize demonstrated research in the field of diabetes, taking into consideration independence of thought and originality.

Eligibility: Any investigator in an appropriate field of work closely related to diabetes who is less than forty years of age on January 1 of the year in which the award is made. The research will not necessarily be judged in comparison to the work of more mature and experienced workers. The candidate should be a resident of the United States or Canada.

Nominations: Nominations for the award will be solicited from the members of the American Diabetes Association. Such nominations will be requested by repeated notices to be published in DIABETES. Names of nominees will be sent to the Chairman of the Committee on Scientific Awards and must be received before January 1 of the year of the award. The nomination should be accompanied by full information concerning the nominee's personality, training and research work. Six copies of each item should be submitted. No member may send in more than one nomination. A list of the nominees' publications, if any, and six copies of the publication or manuscript for which the award is to be given should also accompany the nomination. At the discretion of the Committee on Scientific Awards, the award may be given for work published during the year prior to January 1 of the same year of the award. The nominee should be actively engaged at that time in the line of research for which the award is to be made.

Announcement: The name of the winner will be announced in the program of the Annual Meeting of the Association, and the award presented at that meeting. The winner, subject to the approval of the Committee on Scientific Programs, will be invited to present a paper on his work. Papers considered for the award must be submitted with the idea that they will be published in whole or in part in DIABETES if found acceptable to the Editor and/or Editorial Board. If the Committee should decide that no outstanding work has been presented for this consideration, the award will not be made.

Award: In addition to the monetary award and the medal, traveling expenses will be given to make it possible for the recipient to receive his award in person at the Annual Meeting.

20TH ANNUAL MEETING

The American Diabetes Association will hold its Twentieth Annual Meeting in Miami Beach, Florida, June 11-12, 1960, at the Hotel Deauville. Further information will be published in subsequent issues of the Journal.

NOVEMBER 15 DEADLINE FOR ADA RESEARCH FELLOWSHIP APPLICATIONS

The Committee on Research and Fellowships of the American Diabetes Association will award at least one new Fellowship for the academic year 1960-61 (July 1, 1960—June 30, 1961). Applications may be obtained by writing Mr. J. Richard Connelly, Executive Director, and should be filled out and returned before the deadline of Nov. 15, 1959.

DIABETES WEEK NOVEMBER 15-21

Affiliate Associations and Committees on Diabetes of County and State Medical Societies are urged to begin planning their Public Education and Detection programs now, well in advance of Diabetes Week, which in accordance with custom will be observed the week before Thanksgiving. The Organizational Kit was mailed August 27, and an announcement concerning the availability of testing materials and reagents was sent out August 28. These will be followed by a Newspaper Publicity Kit and a TV-Radio Unit. Report forms will be mailed just prior to Diabetes Week.

Address your requests for information concerning available services and supplies to Louis K. Alpert, M.D., Chairman of the Committee on Public Education and Detection, American Diabetes Association, Inc., 1 East 45th St., New York 17, N.Y.

For a preview of the new Diabetes Week poster in black and white, see page A-6 of this issue of the Journal. In its original form, the poster is black, white, red and yellow.

NEW MEMBERS

The following were elected as of Sept. 1, 1959:

Active

District of Columbia	
Biben, Lewis H.	Washington
Crowell, Jack	Washington
Illinois	
Goldstein, Maurice S.	Chicago
Whalen, Charles P.	Kankakee
Maryland	
Hurdle, Seth H.	Salisbury
Segal, Stanton	Bethesda
Shear, Joseph	Baltimore
Massachusetts	
Goodner, Charles J.	Boston
Minnesota	
Hatfield, Clinton B.	Minneapolis
Hedrick, William L.	Minneapolis
New York	
Greenberg, Wayne V.	New York City
North Carolina	
White, Jefferson E., Jr.	Durham
Ohio	
Landau, Bernard R.	Cleveland
Pennsylvania	
Brody, William	Philadelphia
Feinberg, David H.	Easton
Jenson, William K.	Philadelphia
Washington	
Pace, William R., Jr.	Seattle

U. S. Possessions

Puerto Rico

Haddock, Lillian	Rio Piedras

Other Countries

Brazil

Wajchenberg, Bernardo L.	Sao Paulo

Canada

Brunet, Jacques	Quebec City
Ezrin, Calvin	Toronto
Plamondon, Charles A.	Quebec City
Rebhan, Augusta W.	Toronto

England

Vallance-Owen, John	Newcastle-on-Tyne

NEWS OF AFFILIATE ASSOCIATIONS

The FLORIDA DIABETES ASSOCIATION will hold its Seventh Annual Session Thursday and Friday, Oct. 29-30, at the Balmoral Hotel, Miami Beach, Florida. Cooperating organizations will be the Medical Postgraduate Course Committee of the Florida Medical Association, the Florida State Board of Health, and the Division of Postgraduate Education, College of Medicine, University of Florida.

The program for the Thursday sessions, moderated by Joseph J. Lowenthal, M.D., President, and L. L. Parks, M.D., will include: "What Constitutes Diabetes and the Prediabetic State in Man?" by Jerome W. Conn, M.D., Ann Arbor; "Insulin and Protein Metabolism," by Francis D. W. Lukens, M.D., Philadelphia; "Studies on the Etiology of Cushing's Syndrome," by Nicholas F. Christy, M.D., New York; "Hormonal Control of Fatty Acid Metabolism," by Bernard H. Marks, M.D.; "Connective Tissue Acid Mucopolysaccharides and Their Possible Significance in Endocrine Disorders," by Andrew E. Lorince, M.D.

Friday's program will include: "Assessment of Activity of Sulfonylureas, Clinical and Experimental," by Dr. Lukens; "Pathophysiology of Hypopituitarism," by Dr. Christy; "Kimmelstiel Wilson Disease," by George F. Schmitt, Jr., M.D.; "Primary Aldosteronism, Clinical Considerations and Results to Date," by Dr. Conn; and "A Philosophy of Diabetes," by Dr. Lukens. Moderators for Friday's Sessions will be A. Gorman Hills, M.D., and Grover C. Collins, M.D., President-Elect, Florida Diabetes Association.

There will be a registration fee of $25.00 for the course.

The MICHIGAN DIABETES ASSOCIATION will hold an afternoon and dinner meeting Oct. 2, 1959, at the Pantlind Hotel —Civic Auditorium in Grand Rapids. The program for the afternoon session, with Ralph L. Fitts, M.D., presiding, will include: "Early Diagnosis of Diabetes," by Stefan S. Fajans, M.D.; "Eye Complications of Diabetes," by John B. Bryan, M.D.; "Neurological Complications of Diabetes," by John Sterling Meyers, M.D.; "Planning the Diabetic Diet: I. Prescription," by Keats L. Vining, Jr., M.D.; "Calculating the Diet," by Mary M. Harrington, M.A.; and "Practical Use of Hypoglycemic Agents," by Frank S. Perkin, M.D., President, Michigan Diabetes Association. A panel on "Problems in the Practical Management of Diabetes," moderated by L. F. Segar, M.D., will include William L. Lowrie, M.D., George C. Thosteson, M.D., Dr. Fajans, and Franklyn W. Baske, M.D. Speaker at the evening session with Dr. Perkin presiding, will be William R. Kirtley, M.D., Indianapolis. His subject will be "What the Physician Can Expect in the Future for the Treatment of Diabetes."

The NEW YORK DIABETES ASSOCIATION will hold its Seventh All-Day Symposium entitled "Changing Basic and Clinical Concepts of Diabetes Mellitus" on Friday, Oct. 16, 1959, at the Hunter College Playhouse Auditorium, New York.

The morning session, 9:00 a.m. to 12 noon, is designated as the "Basic Science Panel," with Francis D. W. Lukens, M.D., as moderator. The program will include: James B. Field, M.D., Bethesda, "The Effect of Humoral and Tissue Factors on Insulin Action"; Bruno W. Volk, M.D., and Sydney S. Lazarus, M.D., New York, "The Effect of Insulinogenic Agents on the Pancreatic Islets"; George F. Cahill, Jr., M.D., and Francis C. Wood, Jr., M.D., Boston, "Fatty Acid Metabolism: Some Control Factors in Normal Subjects and in Diabetics"; Philip H. Henneman, M.D., and Dorothy Henneman, M.D., Jersey City, "Metabolic Effects of Human Growth Hormone"; John Logothetopoulos, M.D., B. Sharma, M.D., J. M. Salter, M.D., and Charles H. Best, M.D., Toronto, "Glucagon Diabetes." There is to be a special lecture by C. R. Park, M.D., Nashville, on "The Action of Insulin."

The afternoon session beginning at 2:00 p.m. will be the "Clinical Panel," with Martin G. Goldner, M.D., the moderator. The program will include: Stefan S. Fajans, M.D., Ann Arbor, "Prediabetes"; Max Miller, M.D., Cleveland, "The Problem of Classification of Diabetes"; T. B. Van Itallie, M.D., New York, "Diabetic-like States"; and Thaddeus Danowski, M.D., Pittsburgh, "Newer Aspects of Dietary and Drug Management." Questions and comments will be invited.

Physicians, medical students and other professional personnel interested in diabetes are invited to attend. No fee will be charged, but advance registration is required and may be made by calling or writing the New York Diabetes Association, 104 East 40th St., New York 16, N.Y., OX 7-7760. Admission will be by ticket only.

NEWS NOTES

ADA MEMBERS TO PARTICIPATE IN POSTGRADUATE COURSES

Among the Officers of Instruction at Postgraduate Course No. 1 arranged by the American College of Physicians, Autumn-Winter, 1959-60, "Selected Topics in Internal Medicine," to be held Sept. 28-Oct. 2, 1959, at Georgetown University School of Medicine, Washington, D.C., will be Samuel P. Asper, Jr., M.D., of Baltimore ("New Thyroid Agents"); and John Eager Howard, M.D., Baltimore ("Approach to the Diagnosis of Pheochromocytoma").

"Internal Medicine—Selected Subjects," is the title of Course No. 6 to be held at the Henry Ford Hospital, Detroit, Jan. 25-29, 1960. Among the Officers of Instruction will be: John B. Bryan, M.D., ("Sign-posts in Diabetes") and Fred W. Whitehouse, M.D., ("Electrolyte Problems").

Titled "Recent Advances in Metabolic Diseases," Course No. 7 will be held February 8-12, at The Mount Sinai Hospital, New York. The following will be Officers of Instruction:

David Adlersberg, M.D., ("Idiopathic Hypercholesterolemia and Hyperlipemia" and "The Malabsorption Syndrome"); Jerome W. Conn, M.D., Ann Arbor ("Spontaneous Hypoglycemia," and "Primary Aldosteronism"); Henry Dolger, M.D., ("Current Status of the Oral Hypoglycemic Agents"); Max Ellenberg, M.D., ("Diabetic Neuropathy"); J. Lester Gabrilove, M.D., ("Cushing's Syndrome," and "Myxedema: Primary and Secondary"); and F. Raymond Keating, Jr., M.D., Rochester, Minnesota ("Present Status of Thyroid Function Tests"). Drs. Conn, Dolger and Ellenberg will take part in a panel discussion on diabetes and hypoglycemia.

LECTURES ON APPLIED NUTRITION AND METABOLISM

The Home for the Jewish Aged, in cooperation with the Committee on Nutrition and Metabolism of the Philadelphia County Medical Society and the National Vitamin Foundation, is sponsoring a series of lectures on nutrition and metabolism as they relate to specific medical problems in the aged. The following program will be given:

Oct. 11, 1959: "The Geriatric Patient—Nutritional Requirements," Robert W. Hillman, M.D., New York.

Nov. 11, 1959: "General Therapeutic Nutrition with Emphasis on Obesity," by Herbert Pollack, M.D., New York.

Dec. 9, 1959: "The Relation of Nutrition to Cardiovascular Disease," by Richard W. Vilter, M.D., Cincinnati.

NUTRITION EDUCATION SYMPOSIUM

The Commission on Cardiovascular and Metabolic Diseases of the State of Pennsylvania, in cooperation with the Committee on Nutrition and Metabolism of the Philadelphia County Medical Society and the National Vitamin Foundation, is sponsoring a symposium for interns, residents, and practicing physicians in the Philadelphia area on nutritional and metabolic considerations in disease. The symposium will be held at the Philadelphia General Hospital, Mills Auditorium, Oct. 21, 1959, at 8:30 p.m. The program will be moderated by Michael G. Wohl, M.D., and will include: Paul Gygorgy, M.D., "The Present Controversy Regarding Protein Nutrition"; Thomas Machella, M.D., "Nutritional Aspects of Gastric Disease"; Robert G. Ravdin, M.D., "The Role of Nutrition in the Pre- and Post-operative Care of the Surgical Patient"; William H. Sebrell, Jr., M.D., New York, "Vitamins in the Practice of Medicine"; and Robert S. Goodhart, M.D., New York, "Summarization."

COLLOQUIUM ON DIABETES

The Department of Experimental Medicine and the Diabetic Clinic of Guy's Hospital and Medical School presented a Colloquium on Diabetes on July 24-25, 1959, in London. Henry Dolger, M.D., New York, served as chairman of the final session. Other members of the American Diabetes Association who took part in the program were: Prof. K. Oberdisse, Düsseldorf ("Individual Nutrition History from Patients Treated with Sulfonylurea"); Dr. W. Oakley, London ("Prednisone in Insulin-resistant Diabetes"); and R. E. Dolkart, M.D., Chicago ("Glucose Metabolism in Hepatectomized Dogs").

Prof. W. J. H. Butterfield, London, who chaired the first session and also spoke on "Peripheral Metabolism in Diabetes," has been formally installed in the Chair of Experimental Medicine of Guy's Hospital.

PERSONALS

CHARLES H. BEST, M.D., presented the Annual Lecture of the Society for Endocrinology in London on June 23, 1959. On this occasion, he was presented with the first Dale Medal, which has been struck in honor of Sir Henry Dale, O.M., F.R.S.

During the past summer, Dr. Best lectured at the joint meeting of the Canadian Medical Association and the British Medical Association in Edinburgh, July 18-24, 1959, at which time he received the honorary degree of Doctor of Laws from the University of Edinburgh. Dr. Best also lectured in England on the tenth anniversary of The Ciba Foundation at a symposium on "Significant Trends in Medical Research."

In September, Dr. Best will receive the honorary degree of Doctor of Science from Northwestern University on the occasion of the University's Centennial Celebration.

MORRIS J. ROBIN, M.D., MARK J. MARKHAM, M.D., and HAROLD RIFKIN, M.D., will be Officers of Instruction at Postgraduate Courses in Clinical Medicine given at Montefiore Hospital, September 1959 to June 1960. The courses will be given in affiliation with Columbia University.

SAMUEL SOSKIN, M.D., PH.D., spoke on "Newer Findings in Metabolism" at a session on "Weight Control" during the 42nd Annual Meeting of The American Dietetic Association held in Los Angeles Aug. 25-28, 1959.

RUSSELL M. WILDER, M.D., Rochester, Minnesota, was named an honorary member of The American Dietetic Association at its annual banquet on August 27 "for his contributions to the scientific knowledge, technical skills and cultural growth of the profession of dietetics." Prior to this year, only ten other persons distinguished in fields related to nutrition have been honored in this way. Dr. Wilder had delivered an address on diet therapy previously that day, entitled "Adventures among the Islands of Langerhans." He is an Honorary Member of the American Diabetes Association as well a past President.

HSIEN WU, PH.D., Brookline, Massachusetts, biochemist who collaborated in the development of the Folin-Wu method of blood sugar determination, died August 8 at the age of sixty-five. Until his retirement in 1953, Dr. Wu was on the faculty of the University of Alabama Medical School, which he had joined in 1949. Before that he had taught at the Peiping Union Medical School in China for twenty years, heading the biochemistry department.

Born in Foochow, China, Dr. Wu came to this country in 1911. He graduated from Massachusetts Institute of Technology in 1916. After receiving a Doctor of Philosophy degree in biochemistry from the Harvard Medical School in 1920, he worked closely with Dr. Otto Folin. In 1922, Dr. Wu left Harvard for China. He served the Chinese Government during World War II.

NECROLOGY

ALEXANDER ELLIS, Collingswood, New Jersey, born Dec. 28, 1895.

J. A. SHELLY, Ambler, Pennsylvania, born Oct. 28, 1891.